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(71) Applicant (for all designated States except US):
WARNER-LAMBERT COMPANY LLC [US/US];
201 Tabor Road, Morris Plains, NJ 07950 (US).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **GAUDILLIERE**,
Bernard [FR/FR]; 28, rue de Zillina, F-92000 Nanterre
(FR). **JACOBELLI**, **Henry** [FR/FR]; 65, avenue du
Général de Gaulle, F-91550 Paray Vieille Poste (FR).

(74) Agents: **HIRSCH**, Denise et al.; Pfizer PGRD, Fresnes
Laboratories, 3-9, rue de la Loge, Boîte postale 100,
F-94265 Fresnes Cedex (FR).

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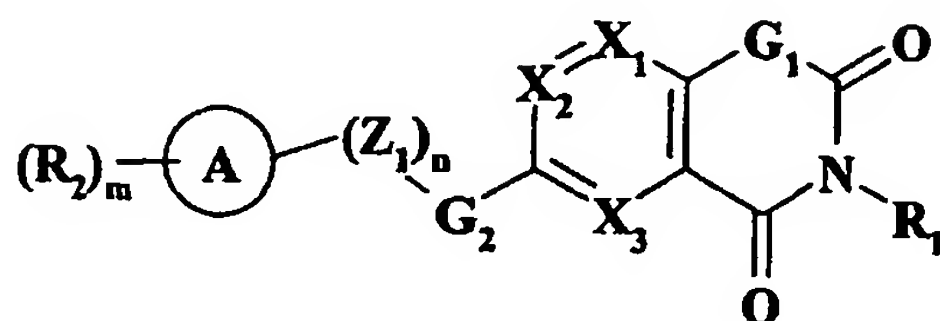
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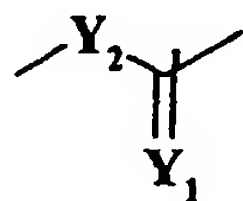
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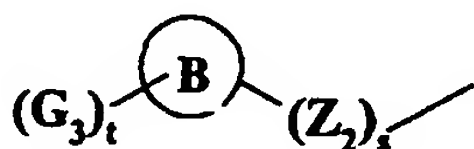
(54) Title: THIAZINE AND OXAZINE DERIVATIVES AS MMP-13 INHIBITORS FOR TREATING ARTHRITIS



(I)



(i/a)



(i/b)

(57) Abstract: A compound selected from those of formula (I): wherein: • X₁, X₂, and X₃ represent nitrogen or -CR₃ in which R₃ represents hydrogen, alkyl, amino, alkylamino, dialkylamino, hydroxy, alkoxy, or halogen, • G₁ represents oxygen or S(O)_p in which p is from 0 to 2, • G₂ represents carbon-carbon triple bond, C=O, C=S, S(O)_q in which q is from 0 to 2, or a group of formula (i/a): in which Y₁ and Y₂ are as defined in the description, • n is from 0 to 6, Z₄ represents -CR₄R₅, wherein R₄ and R₅ are as defined in the description, • A represents 5- or 6-membered monocycle or bicycle aryl, heteroaryl, cycloalkyl, or heterocycloalkyl, • R₁ represents hydrogen, alkyl, alkenyl, alkynyl, (these groups may be optionally substituted as defined in the description) or the group of formula (i/b): in which s, Z₂, B, t and G₃ are as defined in the

description, and optionally, its optical isomers, N-oxide, and addition salts thereof with a pharmaceutically-acceptable acid or base, and medicinal products containing the same are useful as specific inhibitors of type-13 matrix metalloprotease, for the treatment of i.a arthritis and cancer.

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TITLE OF THE INVENTION

THIAZINE AND OXAZINE DERIVATIVES AS MMP-13 INHIBITORS FOR TREATING ARTHRITIS

FIELD OF THE INVENTION

5 The present invention relates to novel thiazine and oxazine derivatives which are useful for preparing medicinal products for treating complaints involving a therapy with a matrix metalloprotease-13 (MMP-13) inhibitor. These medicinal products are useful in particular for treating certain inflammatory conditions such as rheumatoid arthritis or osteoarthritis, as well as certain proliferative conditions such as cancers.

TECHNOLOGICAL BACKGROUND OF THE INVENTION

0 Matrix metalloproteases (MMPs) are enzymes which are involved in the renewal of extracellular matrix tissue, such as cartilage, tendons and joints. MMPs bring about the destruction of the extracellular matrix tissue, which is compensated for, in a non-pathological physiological state, by its simultaneous regeneration.

5 Under normal physiological conditions, the activity of these extremely aggressive peptidases is controlled by specialized proteins which inhibit MMPs, such as the tissue inhibitors of metalloprotease (TIMPs).

Local equilibrium of the activities of MMPs and of TIMPs is critical for the renewal of the extracellular matrix. Modifications of this equilibrium which result in an excess of active MMPs, relative to their inhibitor, induce a pathological destruction of cartilage, which is observed in particular in rheumatoid arthritis and in osteoarthritis.

10 In pathological situations, an irreversible degradation of articular cartilage takes place, as is the case in rheumatic diseases such as rheumatoid arthritis or osteoarthritis. In these pathologies, the cartilage degradation process predominates, leading to a destruction of the tissue and resulting in a loss of function.

15 At least twenty different matrix metalloproteases have been identified to date and are subdivided into four groups, the collagenases, the gelatinases, the stromelysins and the membrane-type MMPs (MT-MMPs), respectively.

Matrix metalloprotease-13 (MMP-13) is a collagenase-type MMP which constitutes the predominant collagenase observed during osteoarthritis, in the course of which pathology the chondrocyte directs the destruction of cartilage.

There is a need in the prior art for novel MMP inhibitors, more particularly for
 5 MMP-13 inhibitors, in order to prevent and/or correct the imbalance in the renewal of extracellular matrix tissue, such as arthritis, rheumatoid arthritis, osteoarthritis, osteoporosis, periodontal diseases, inflammatory bowel disease, psoriasis, multiple sclerosis, cardiac insufficiency, atherosclerosis, asthma, chronic obstructive pulmonary diseases (COPD), age-related macular degeneration (ARMD) and cancer.

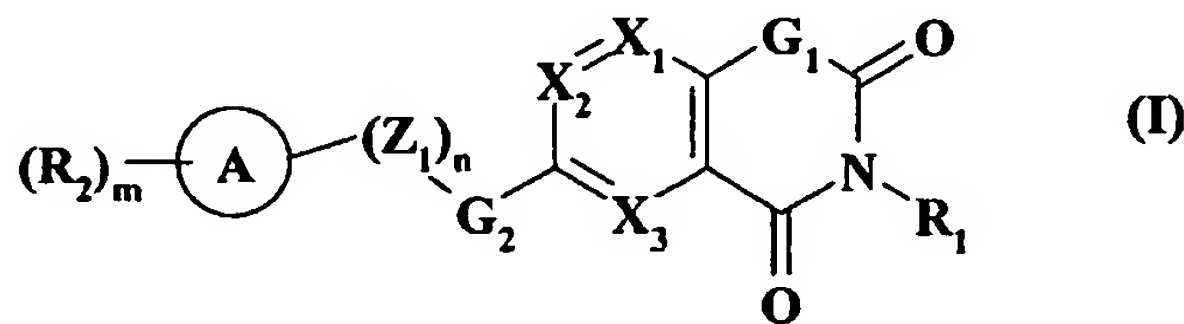
0 MMP-inhibitor compounds are known. Most of these MMP-inhibitors are not selective for a single MMP, such as those described by Montana and Baxter (2000) or by Clark et al. (2000).

There is also a need in the prior art for novel inhibitors that are active on matrix metalloprotease-13, in order to enrich the therapeutic arsenal that can be used for treating
 5 pathologies associated with the destruction of the extracellular matrix and with cancer.

SUMMARY OF THE INVENTION

The applicant has identified novel thiazine and oxazine derivatives that are matrix metalloprotease inhibitors, and more specifically compounds that are selective MMP-13 inhibitors.

0 More specifically, the present invention relates to compounds of formula (I) :



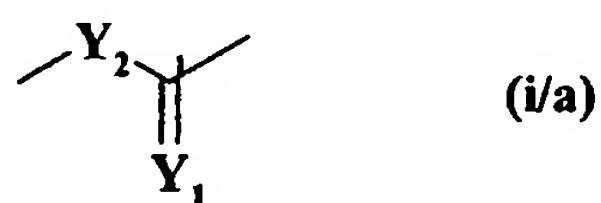
wherein:

- X₁, X₂, and X₃, independently of each other, represent a nitrogen atom or a group -CR₃ in which R₃ represents a group selected from hydrogen, (C₁-C₆)alkyl, amino,
 5 mono(C₁-C₆)alkylamino, di(C₁-C₆)alkylamino, hydroxy, (C₁-C₆)alkoxy, and halogen,

it being understood that not more than two of the groups X_1 , X_2 and X_3 simultaneously represent a nitrogen atom,

- G_1 represents an oxygen atom or a group $S(O)_p$ in which p represents an integer from 0 to 2 inclusive,

5 • G_2 represents a group selected from carbon-carbon triple bond, $C=O$, $C=S$, $S(O)_q$ in which q represents an integer from 0 to 2 inclusive, or a group of formula (i/a):



in which the carbon atom with the number 1 is attached to the bicycle of the compound of formula (I), Y_1 represents a group selected from oxygen, sulphur, $-NH$ and $-N(C_1-C_6)alkyl$,
 .0 and Y_2 represents a group selected from oxygen, sulphur, $-NH$ and $-N(C_1-C_6)alkyl$,

- n represents an integer from 0 to 6 inclusive,

• Z_1 represents $-CR_4R_5$, wherein R_4 and R_5 , identical or different independently of each other, represent a group selected from hydrogen, $(C_1-C_6)alkyl$, trihalogeno $(C_1-C_6)alkyl$, halogen, amino, mono $(C_1-C_6)alkylamino$, di $(C_1-C_6)alkylamino$ in which each alkyl moiety is identical or different, $-OR_6$, $-SR_6$, and $-C(=O)OR_6$, in which R_6 is hydrogen atom or $(C_1-C_6)alkyl$, and

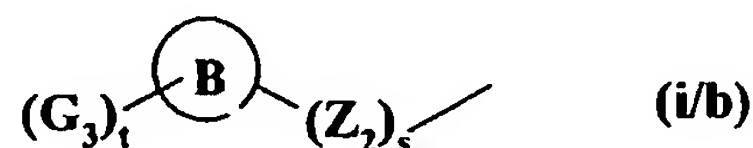
- wherein when n is greater than or equal to 2, the hydrocarbon chain Z_1 optionally contains one to two isolated or conjugated multiple bonds,

- and/or wherein when n is greater than or equal to 2 one of said $-CR_4R_5$ may be replaced
 !0 with a group selected from oxygen, $S(O)_r$ in which r represents an integer from 0 to 2 inclusive, $-NH$ and $-N(C_1-C_6)alkyl$,

- A represents a group selected from aryl, heteroaryl, cycloalkyl, and heterocycloalkyl, these groups being a 5- or 6-membered monocycle, or bicycle itself composed of two 5- or 6-membered monocycles,

- R_1 represents a group selected from :

- hydrogen,
- (C_1-C_6) alkyl, (C_2-C_6) alkenyl, (C_2-C_6) alkynyl, these groups may be optionally substituted with one or more groups, which may be identical or different independently of each other, selected from amino, cyano, trihalogeno (C_1-C_6) alkyl, cycloalkyl, $-C(=O)NR_7R_8$, $-C(=O)OR_7$, OR_7 , and SR_7 , in which R_7 and R_8 , which may be identical or different independently of each other, represent hydrogen or (C_1-C_6) alkyl,
- and the group of formula (i/b) :



- ✓ in which s is an integer from 0 to 8 inclusive,

- ✓ Z_2 represents $-CR_9R_{10}$ wherein R_9 and R_{10} , identical or different independently of each other, represent a group selected from hydrogen, (C_1-C_6) alkyl, phenyl, trihalogeno (C_1-C_6) alkyl, halogen, amino, OR_6 , SR_6 and $-C(=O)OR_6$ in which R_6 is as defined hereinbefore, and

- wherein when s is greater than or equal to 2, the hydrocarbon chain Z_2 optionally contains one or two isolated or conjugated multiple bonds,
- and/or wherein when p is greater or equal to 2, one of said $-CR_9R_{10}$ may be replaced with a group selected from oxygen, $S(O)_u$ in which u is an integer from 0 to 2 inclusive, $-NH$, $-N(C_1-C_6)$ alkyl, and carbonyl,

- ✓ B represents a group selected from aryl, heteroaryl, cycloalkyl, and heterocycloalkyl, these groups being a 5- or 6-membered monocycle, or bicycle itself composed of two 5- or 6-membered monocycles,

- ✓ t is an integer from 0 to 7 inclusive,

- ✓ the group(s) G_3 , which may be identical or different independently of each other, is (are) selected from (C_1-C_6) alkyl, halogen, CN, NO_2 , CF_3 , OCF_3 , $-(CH_2)_kNR_{11}R_{12}$,

$-N(R_{11})C(=O)R_{12}$, $-N(R_{11})C(=O)OR_{12}$, $-N(R_{11})SO_2R_{12}$, $-N(SO_2R_{11})_2$, $-OR_{11}$,
 $-S(O)_{k1}R_{11}$, $-SO_2-N(R_{11})-(CH_2)_{k2}-NR_{12}R_{13}$, $-(CH_2)_kSO_2NR_{11}R_{12}$,
 $-X_4(CH_2)_kC(=O)OR_{11}$, $-(CH_2)_kC(=O)OR_{11}$, $-C(=O)O-(CH_2)_{k2}-NR_{11}R_{12}$,
 $-C(=O)O-(CH_2)_{k2}-C(=O)OR_{14}$, $-X_4(CH_2)_kC(=O)NR_{11}R_{12}$, $-(CH_2)_kC(=O)NR_{11}R_{12}$,
 $-R_{15}-C(=O)OR_{11}$, $-X_5-R_{16}$, and $-C(=O)-R_{17}-NR_{11}R_{12}$ in which :

- X_4 represents a group selected from oxygen, sulphur optionally substituted by one or two oxygen, and nitrogen substituted by a hydrogen or a (C₁-C₆)alkyl group,

- k is an integer from 0 to 3 inclusive,

- k_1 is an integer from 0 to 2 inclusive,

0 - k_2 is an integer from 1 to 4 inclusive,

- R_{11} , R_{12} and R_{13} , which may be identical or different independently of each other, are selected from hydrogen and (C₁-C₆)alkyl,

5 - R_{14} represents a group selected from (C₁-C₆)alkyl, $-R_{17}-NR_{11}R_{12}$, $-R_{17}-NR_{11}-C(=O)-R_{17}-NR_{12}R_{13}$, and $-C(=O)O-R_{17}-NR_{11}R_{12}$ in which R_{17} represents a linear or branched (C₁-C₆)alkylene group, and R_{11} , R_{12} and R_{13} are as defined hereinbefore,

- R_{15} represents a (C₃-C₆)cycloalkyl group,

10 - X_5 represents a group selected from a single bond, $-CH_2-$, oxygen, sulphur optionally substituted by one or two oxygen, and nitrogen substituted by hydrogen or (C₁-C₆)alkyl,

- R_{16} represents a group selected from :

- o a 5- or 6-membered monocyclic aryl or heteroaryl, which is optionally substituted by one or more groups, which may be identical or different independently of each

other, selected from (C₁-C₆)alkyl, halogen, hydroxy, cyano, tetrazolyl, amino, and -C(=O)OR₇ wherein R₇ represents hydrogen or (C₁-C₆)alkyl,

- o and a 5- or 6-membered monocyclic cycloalkyl or heterocycloalkyl, which is optionally substituted by one or more groups, which may be identical or different independently of each other, selected from (C₁-C₆)alkyl, halogen, hydroxy, oxo, cyano, tetrazolyl, amino, and -C(=O)OR₇ wherein R₇ represents hydrogen or (C₁-C₆)alkyl,

- m is an integer from 0 to 7 inclusive,

- the group(s) R₂, which may be identical or different independently of each other, is (are) selected from (C₁-C₆)alkyl, halogen, -CN, -NO₂, -SCF₃, -CF₃, -OCF₃, -NR₇R₈, -OR₇, -SR₇, -SOR₇, -SO₂R₇, -(CH₂)_kSO₂NR₇R₈, -X₇(CH₂)_kC(=O)OR₇, -(CH₂)_kC(=O)OR₇, -X₇(CH₂)_kC(=O)NR₇R₈, -(CH₂)_kC(=O)NR₇R₈, and -X₈-R₁₈ in which:

- X₇ represents a group selected from oxygen, sulphur optionally substituted by one or two oxygen, and nitrogen substituted by hydrogen or (C₁-C₆)alkyl,

- k is an integer from 0 to 3 inclusive,

- R₇ and R₈, which may be identical or different independently of each other, are selected from hydrogen and (C₁-C₆)alkyl,

- X₈ represents a group selected from single bond, -CH₂-, oxygen, sulphur optionally substituted by one or two oxygen, and nitrogen substituted by hydrogen or (C₁-C₆)alkyl,

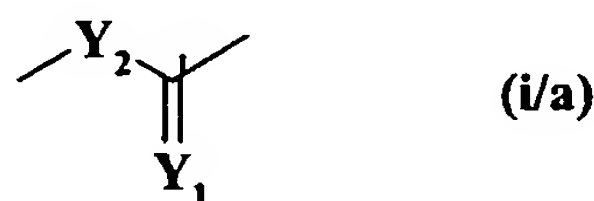
- R₁₈ represents a group selected from phenyl, a 5- or 6-membered monocyclic, heteroaryl, and a 5- or 6-membered monocyclic cycloalkyl, each of these groups being optionally substituted by one or more groups, which may be identical or different independently of each other, selected from (C₁-C₆)alkyl, halogen, hydroxy and amino,

and optionally, their racemic forms, isomers, N-oxides, and pharmaceutically acceptable salts,

and with the proviso that the compound of formula (I) is not 6-(2,4-dioxo-3,4-dihydro-2H-1,3-benzothiazine)-benzoate, 6-phenylthio-2,4-dioxo-3,4-dihydro-2H-1,3-benzothiazine, 6-benzylsulphonyl-2,4-dioxo-3,4-dihydro-2H-1,3-benzothiazine, 6-benzophenone-2,4-dioxo-3,4-dihydro-2H-1,3-benzothiazine and 6-(2,4-dihydroxy)-benzophenone-2,4-dioxo-3,4-dihydro-2H-1,3-benzothiazine.

According to a first embodiment, the invention relates to compounds of formula (I) wherein :

- G_1 represents a sulphur atom,
- G_2 represents a group of formula (i/a):



in which the carbon atom with the number 1 is attached to the bicycle of the compound of formula (I), Y_1 represents an oxygen atom, and Y_2 represents a group -NH,

- $X_1, X_2, X_3, n, Z_1, A, R_1, m$ and R_2 are as defined in formula (I).

According to a second embodiment, the invention relates to compounds of formula (I) wherein :

- G_1 represents an oxygen atom,
- G_2 represents a group of formula (i/a):



in which the carbon atom with the number 1 is attached to the bicycle of the compound of formula (I), Y_1 represents an oxygen atom, and Y_2 represents a group -NH,

- $X_1, X_2, X_3, n, Z_1, A, R_1, m$ and R_2 are as defined in formula (I).

According to a third embodiment, the invention relates to compounds of formula (I) wherein :

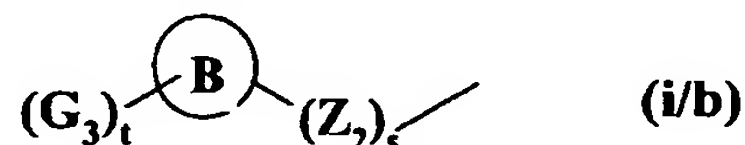
- G_1 represents a sulphur atom,

- G_2 represents a carbon-carbon triple bond,
 - n represents an integer from 1 to 6 inclusive,
- X_1 , X_2 , X_3 , Z_1 , A , R_1 , m and R_2 are as defined in formula (I).

According to a fourth embodiment, the invention relates to compounds of formula (I)
 5 wherein :

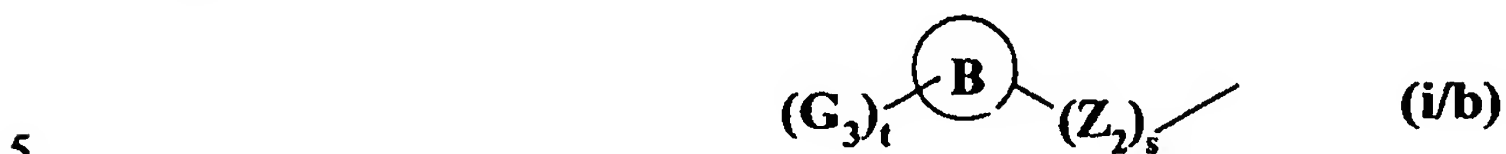
- G_1 represents an oxygen atom,
 - G_2 represents a carbon-carbon triple bond,
 - n represents an integer from 1 to 6 inclusive,
- X_1 , X_2 , X_3 , Z_1 , A , R_1 , m and R_2 are as defined in formula (I).

0 The substituent R_1 that is preferred according to the invention is the group of formula (i/b):



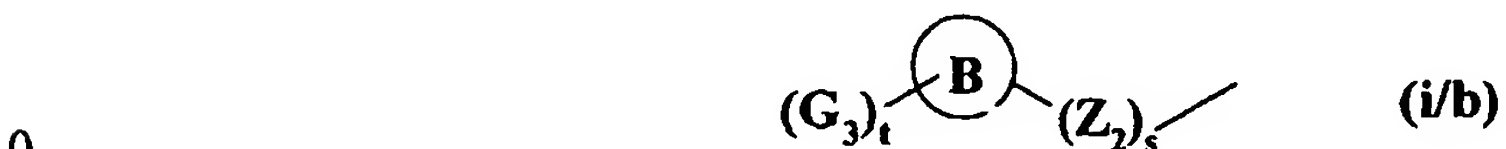
wherein Z_2 , s , B , G_3 and t are as defined in the compound of formula (I).

More particularly, the substituent R_1 that is preferred according to the invention is the group of formula (i/b):



wherein Z_2 represents a group $-\text{CR}_9\text{R}_{10}$ in which R_9 and R_{10} represents each a hydrogen atom, s is equal to one, and B , G_3 , and t are as defined in the compound of formula (I).

More particularly, the substituent R_1 that is preferred according to the invention is the group of formula (i/b):



wherein B represents a phenyl group, t is equal to 0 or 1, and G_3 , when it is present, represents a group selected from OR_{11} , halogen, and $(\text{CH}_2)_k\text{C}(=\text{O})\text{OR}_{11}$ in which R_{11} represents an hydrogen atom or a $(\text{C}_1\text{-C}_6)$ alkyl group and k is equal to zero.

Preferred compounds of the invention are compounds of formula (I) wherein X_1 , X_2 , and X_3 represent each a group $-CR_3$ in which R_3 represents a hydrogen atom.

Other preferred compounds of the invention are compounds of formula (I) wherein X_1 represents a group $-CR_3$ in which R_3 represents a hydrogen atom, X_2 represents a nitrogen atom, and X_3 represents a group $-CR_3$ in which R_3 represents a hydrogen atom.

Advantageously, preferred compounds of the invention are those compounds of formula (I) wherein Z_1 represents $-CR_4R_5$ in which R_4 and R_5 represent each a hydrogen atom, and n is equal to one.

Especially preferred compounds of the invention are compounds of formula (I) wherein A represents a phenyl group, m is equal to zero or one, and R_2 represents a (C_1-C_6) alkoxy group or a hydrogen atom.

In another embodiment, preferred compounds of the invention are compounds of formula (I) wherein A represents a pyridyl group, m is equal to zero or one, and R_2 represents a (C_1-C_6) alkoxy group or a hydrogen atom.

Another especially preferred compounds of the invention are compound of formula (I) wherein A represents an imidazolyl group.

More particularly, the invention relates to the following compounds of formula (I) :

- 3-benzyl-2,4-dioxo-3,4-dihydro-2*H*-benzo[*e*][1,3]thiazine-6-carboxylic acid 4-methoxy benzylamide;
- 3-(4-methoxybenzyl)2,4-dioxo-3,4-dihydro-2*H*-benzo[*e*][1,3]oxazine-6-carboxylic acid 4-methoxybenzylamide;
- and 4-[2,4-dioxo-6-(3-phenyl-prop-1-ynyl)-4*H*-1,3-benzothiazin-3-ylmethyl]-benzoic acid.

The optical isomers, the N-oxides, as well as the addition salts with a pharmaceutically-acceptable acid or base, of the preferred compounds form an integral part of the invention.

The invention also relates to a pharmaceutical composition comprising as active ingredient an effective amount of a compound of formula (I) together with one or more pharmaceutically-acceptable excipients or carriers.

5 Another embodiment of the invention concerns the use of the compound of formula (I) for the preparation of a medicinal product intended for treating a disease involving therapy by inhibition of matrix metalloprotease, and more particularly of type-13 matrix metalloprotease.

0 The invention also relates to a method for treating a living body afflicted with a disease involving a therapy by inhibition of matrix metalloprotease, and more particularly of type-13 matrix metalloprotease, the said method comprising the administration of an effective amount of a compound of formula (I) to a patient in need thereof.

5 A preferred method of treatment according to this invention is treatment of a disease selected from arthritis, rheumatoid arthritis, osteoarthritis, osteoporosis, periodontal diseases, inflammatory bowel disease, psoriasis, multiple sclerosis, cardiac insufficiency, atherosclerosis, asthma, chronic obstructive pulmonary diseases, age-related degeneration and cancers.

More particularly, a preferred method of treatment according to this invention is treatment of disease selected from arthritis, osteoarthritis and rheumatoid arthritis.

DETAILED DESCRIPTION OF THE INVENTION

10 The compounds provided by this invention are those defined in formula (I). In formula (I), it is understood that :

- a (C₁-C₆)alkyl group denotes a linear or branched group containing from 1 to 6 carbon atoms ; example of such groups, without implying any limitation are methyl, ethyl, propyl, isopropyl, tert-butyl, neopentyl, hexyl,

- a (C₂-C₆)alkenyl group denotes a linear or branched group containing from 2 to 6 carbon atoms, and one or more double bonds ; examples of such groups without implying any limitation are vinyl, allyl, 3-buten-1-yl, 2-methyl-buten-1-yl, hexenyl,

5 - a (C₂-C₆)alkynyl group denotes a linear or branched group containing from 2 to 6 carbon atoms, and one or more triple bonds ; examples of such groups without implying any limitation are ethynyl, propynyl, 3-butyn-1-yl, 2-methyl-butyn-1-yl, hexynyl,

- a (C₁-C₆)alkoxy group means the alkyl group as mentioned above bound through an oxygen atom ; examples of such compounds without implying any limitation are methoxy, ethoxy, *n*-propyloxy, *tert*-butyloxy,

0 - a mono(C₁-C₆)alkylamino denotes a amino group substituted by one (C₁-C₆)alkyl group as defined hereinbefore ; example of such groups, without implying any limitation are methyl amino, isobutyl amino, ethylamino,

5 - a di(C₁-C₆)alkylamino denotes a amino group substituted by two (C₁-C₆)alkyl groups as defined hereinbefore, each alkyl group being identical or different ; example of such groups, without implying any limitation are dimethylamino, diethylamino,

- an aryl group denotes an aromatic monocyclic or bicyclic system containing from 5 to 10 carbon atoms, and in the case of a bicyclic system, one of the ring of which is aromatic in character, and the other ring of which may be aromatic or partially hydrogenated ; examples of such groups without implying any limitation are, phenyl, naphthyl, indenyl, benzocyclobutenyl,

10 - a heteroaryl group denotes an aryl group as described above in which 1 to 4 carbon atoms are replaced by 1 to 4 hetero atoms selected from oxygen, sulfur and nitrogen ; examples of such groups without implying any limitation are furyl, thienyl, pyrrolyl, pyrazolyl, pyridyl, pyrimidyl, pyrazinyl, benzofuryl, benzothienyl, indolyl, quinolyl, isoquinolyl, imidazolyl, benzodioxolyl, benzodioxinyl, benzo[1,2,5]thiadiazolyl, benzo[1,2,5]oxadiazolyl,

15 - a cycloalkyl group denotes a monocyclic or bicyclic system containing from 3 to 10 carbon atoms, this system being saturated or partially unsaturated but without aromatic character ; examples of such groups without implying any limitation are cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclooctyl, cycloheptyl, adamantyl, decalanyl, norbornyl,

- a heterocycloalkyl group denotes a cycloalkyl group as defined hereinbefore in which 1 to 4 carbon atoms are replaced by 1 to 4 hetero atoms selected from oxygen, sulfur, and nitrogen,

- a bicycle denotes two fused-monocycle or two bridged-monocycle,

5 - a trihalogeno(C₁-C₆)alkyl group denotes an alkyl group as defined above which contains a trihalogeno group ; examples of such groups without implying any limitation are trifluoromethyl, 2,2,2-trifluoroethyl,

0 - a (C₁-C₇)acyl group denotes an alkyl group or an aryl group as defined above bound through a carbonyl group ; examples of such groups without implying any limitation are acetyl, ethylcarbonyl, benzoyl,

- a multiple bond denotes double bond or triple bond,

- a halogen atom means fluoro, chloro, bromo or iodo,

optical isomers refer to racemates, enantiomers and diastereoisomers.

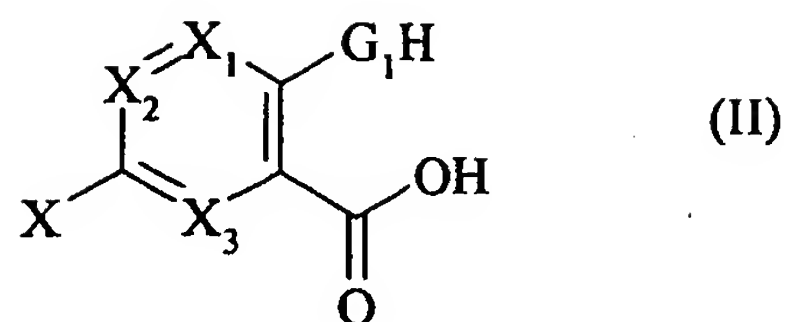
The invention also relates to the pharmaceutically acceptable salts of the compounds of formula (I). A review of the pharmaceutically acceptable salts will be found in *J. Pharm. Sci.*, 1977, 66, 1-19.

Pharmaceutically acceptable acids mean non-toxic mineral or organic acids. Among those there may be mentioned, without implying any limitation, hydrochloric acid, hydrobromic acid, sulfuric acid, phosphonic acid, nitric acid, citric acid, acetic acid, trifluoroacetic acid, 10 lactic acid, pyruvic acid, malonic acid, succinic acid, glutaric acid, fumaric acid, tartaric acid, maleic acid, ascorbic acid, oxalic acid, methanesulfonic acid, camphoric acid, benzoic acid, toluenesulfonic acid, etc...

Pharmaceutically acceptable bases mean non-toxic mineral or organic bases. Among those, there may be mentioned, without implying any limitation, sodium hydroxide, potassium 15 hydroxide, calcium hydroxide, triethylamine, tert-butylamine, dibenzylethylenediamine, piperidine, pyrrolidine, benzylamine, quaternary ammonium hydroxides etc...

The invention also relates to a process for the preparation of compounds of formula (I), which uses as starting material a compound of formula (II):

13



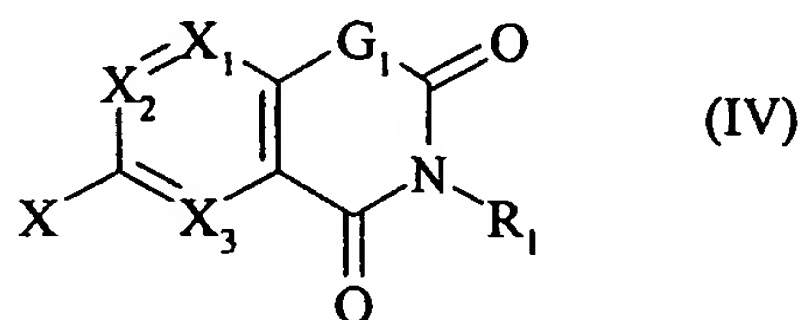
in which X_1 , X_2 , X_3 , and G_1 have the same definitions as the compound of formula (I), and X represents a leaving group selected from halogen, triflate, mesylate, tosylate and SO_2 alkyl,

- 5 compound of formula (II) which is treated in basic medium with an isocyanate compound of formula (III):



in which R_1 has the same definitions as the compound of formula (I),

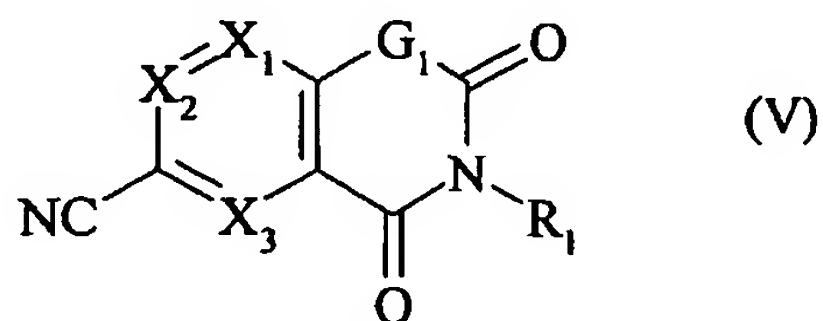
to yield the compound of formula (IV) :



0

in which X_1 , X_2 , X_3 , G_1 , X , and R_1 are as defined hereinbefore,

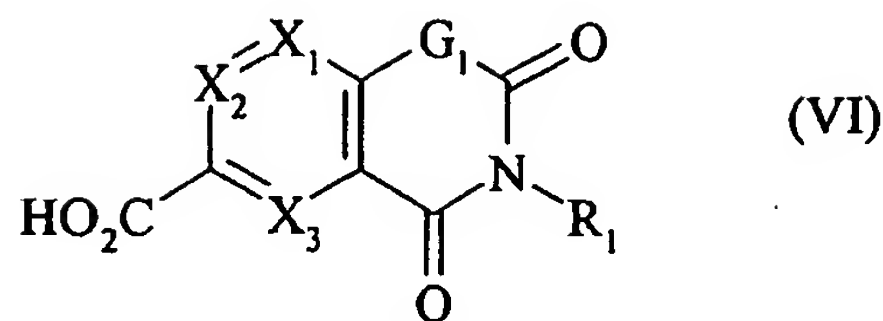
compound of formula (IV) in which the leaving group X is reacted with a cyanocuprate to yield the compound of formula (V) :



- 5 in which X_1 , X_2 , X_3 , G_1 , and R_1 are as defined hereinbefore,

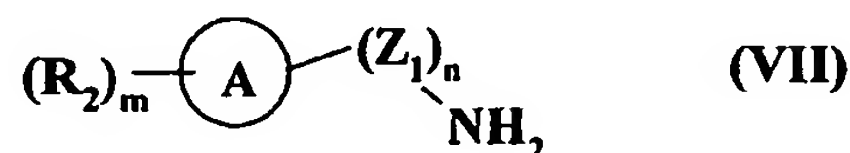
which compound of formula (V) is treated with an acid like sulfuric acid to yield the compound of formula (VI):

14



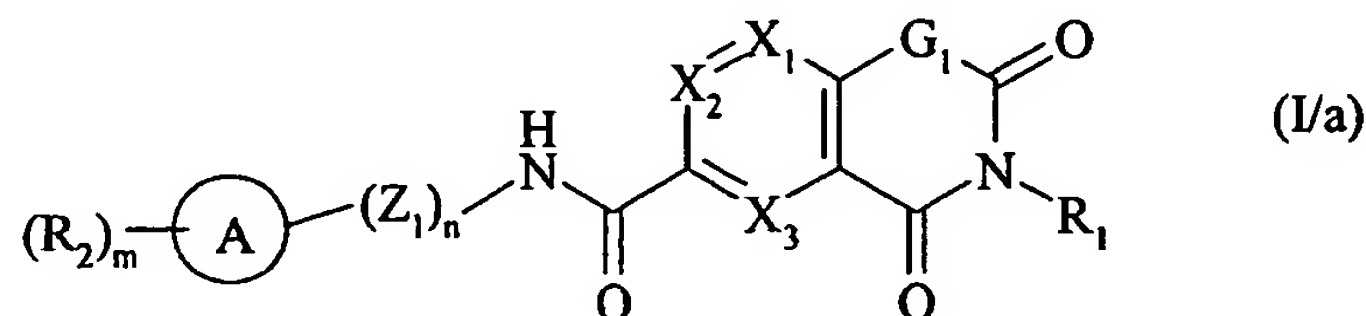
in which X_1 , X_2 , X_3 , G_1 , and R_1 are as defined hereinbefore,

compound of formula (VI) which is treated with a compound of formula (VII):



5 in which Z_1 , R_2 , A , n and m have the same definitions as the compound of formula (I),

by activating the acid function with an activator, in the presence of diisopropylethylamine and a solvent, to yield the compound of formula (I/a) which is a particular case of the compounds of formula (I):



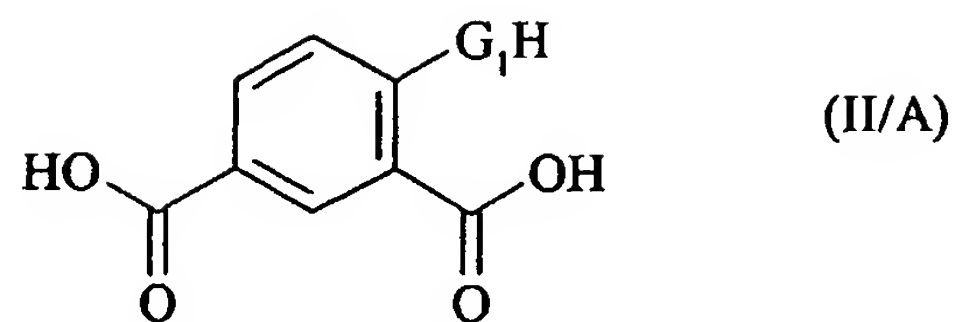
10 in which X_1 , X_2 , X_3 , G_1 , Z_1 , R_1 , R_2 , A , n and m are as defined hereinbefore,

compounds of formula (I/a) constitute some compounds of the invention, which are purified, where appropriate, according to a conventional purification technique, which are separated, where appropriate, into their different isomers according to a conventional separation technique, and which are converted, where appropriate, into addition salts thereof with a pharmaceutically-acceptable acid or base, or into N-oxide thereof.

15

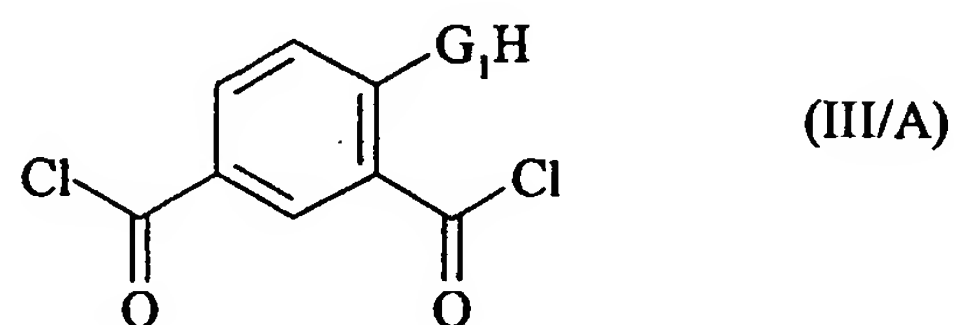
The invention also relates to another process for the preparation of specific compounds of formula (I/a), which are a particular case of compounds of formula (I), which uses as starting material a compound of formula (II/A):

15



in which G_1 has the same definitions as the compound of formula (I),

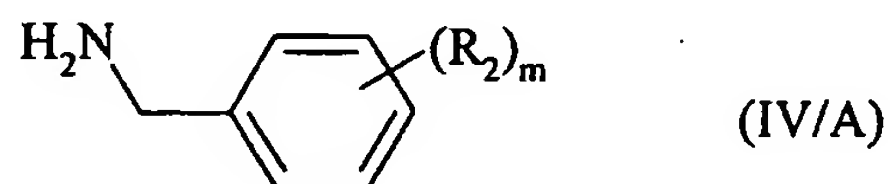
compound of formula (II/A) which is treated with SOCl_2 to yield the compound of formula (III/A) :



5

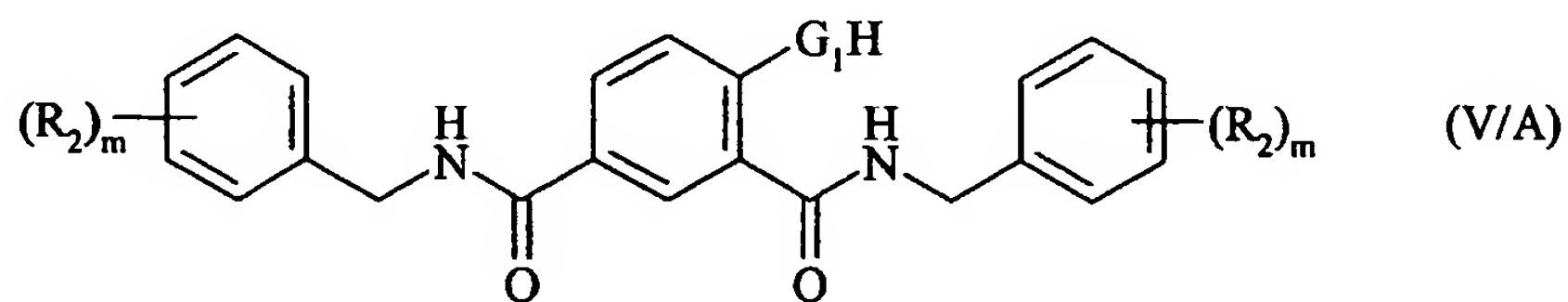
in which G_1 is as defined hereinbefore,

compound of formula (III/A) reacting with a benzylamine derivative of formula (IV/A):



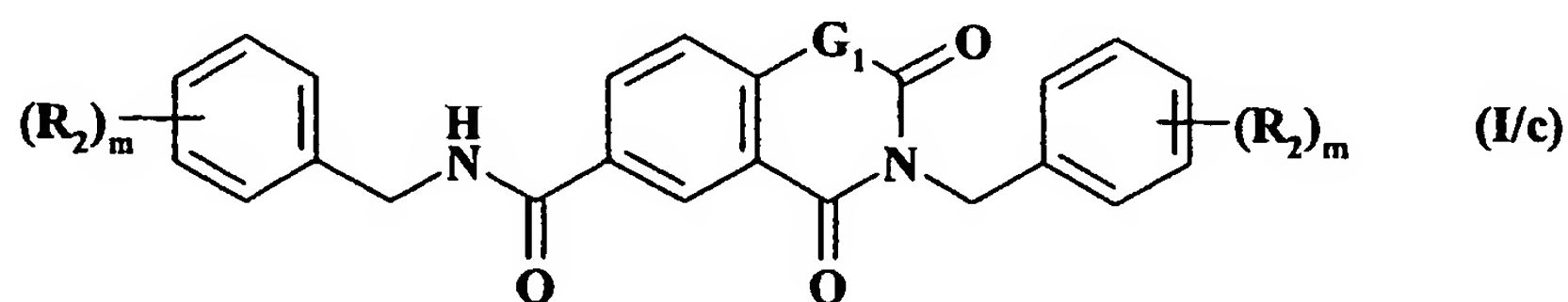
in which R_2 and m are as defined in the compound of formula (I),

0 to yield the compound of formula (V/A):



in which G_1 , m and R_2 are as defined hereinbefore,

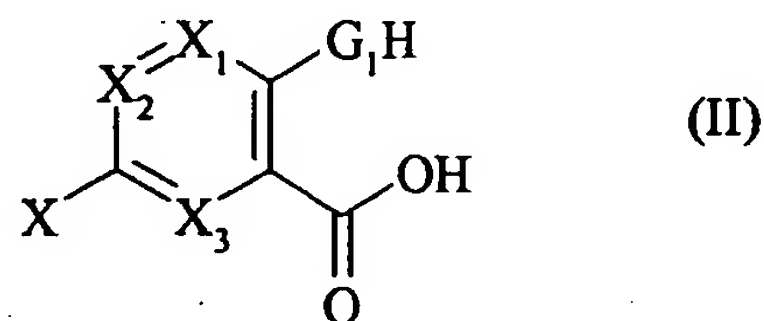
compound of formula (V/A) reacting with a chloroformate compound, to yield the compound of formula (I/c) which is a particular case of the compounds of formula (I):



5

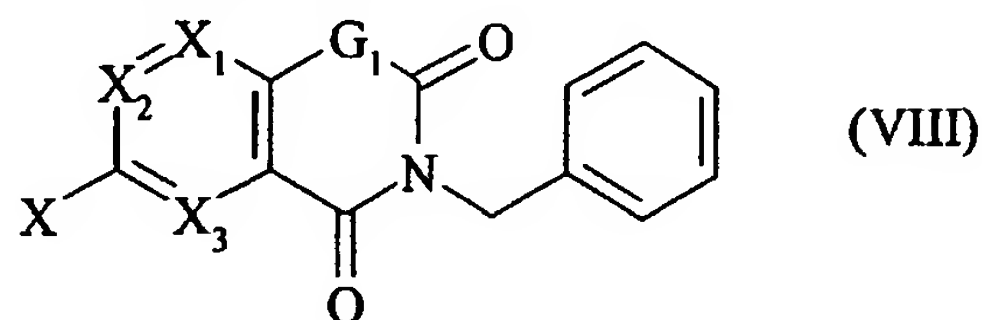
in which G_1 , R_2 and m have the same definitions as the compound of formula (I),
 compounds of formula (I/c) constitute some compounds of the invention, which are
 purified, where appropriate, according to a conventional purification technique, which are
 separated, where appropriate, into their different isomers according to a conventional
 5 separation technique, and which are converted, where appropriate, into addition salts
 thereof with a pharmaceutically-acceptable acid or base, or into N-oxide thereof.

The invention also relates to a process for the preparation of compounds of formula (I),
 which uses as starting material a compound of formula (II):



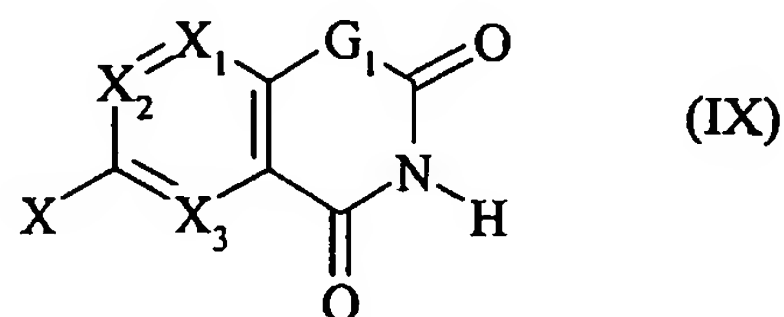
0 in which X_1 , X_2 , X_3 , and G_1 have the same definitions as the compound of formula (I), and
 X represents a leaving group selected from halogen, triflate, mesylate, tosylate and
 SO_2alkyl ,

compound of formula (II) which is treated in basic medium with a benzylisocyanate
 to yield the compound of formula (VIII) :



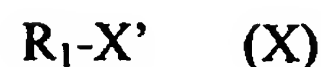
5 in which X_1 , X_2 , X_3 , G_1 , and X are as defined hereinbefore,

compound of formula (VIII) which is treated with $AlCl_3$ in an apolar solvent to yield the
 compound of formula (IX) :



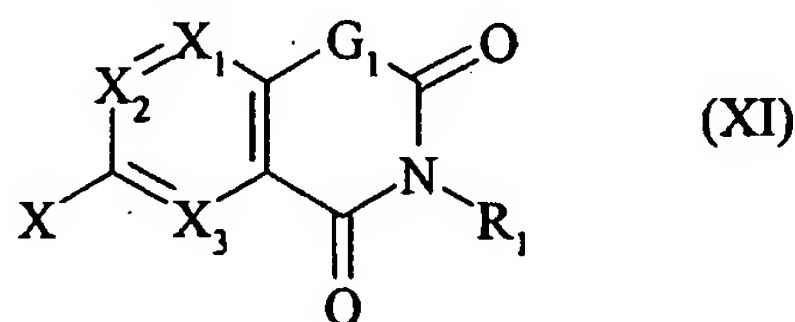
10 in which X_1 , X_2 , X_3 , G_1 , and X are as defined hereinbefore,

which compound of formula (IX) is treated in the presence of an inorganic base with a compound of formula (X):



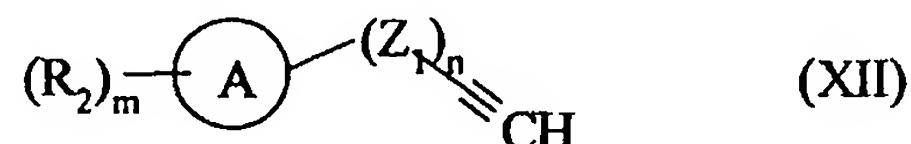
in which R_1 is as defined in the compound of formula (I) and X' represents a leaving group like halogen atom, mesylate, tosylate or triflate group,

to yield a compound of formula (XI) :



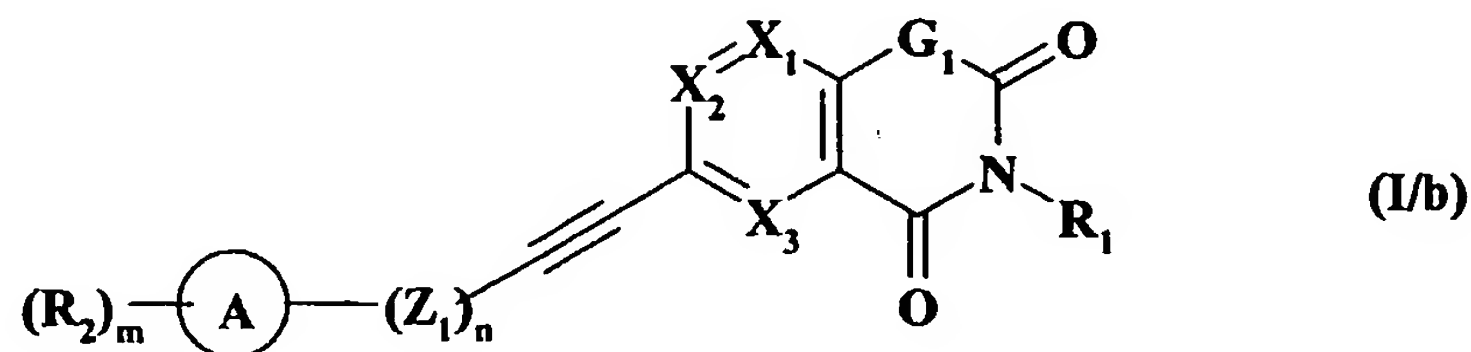
in which X_1 , X_2 , X_3 , G_1 , X and R_1 are as defined hereinbefore,

compound of formula (XI) which is condensed, in the presence of dichlorobis(triphenylphosphine)palladium, copper iodide and *N,N'*-diisopropylethylamine in dimethylformamide, on a compound of formula (XII) :



in which Z_1 , R_2 , A , n and m have the same definitions as the compound of formula (I),

to yield the compound of formula (I/b), which is a particular case of the compound of formula (I):

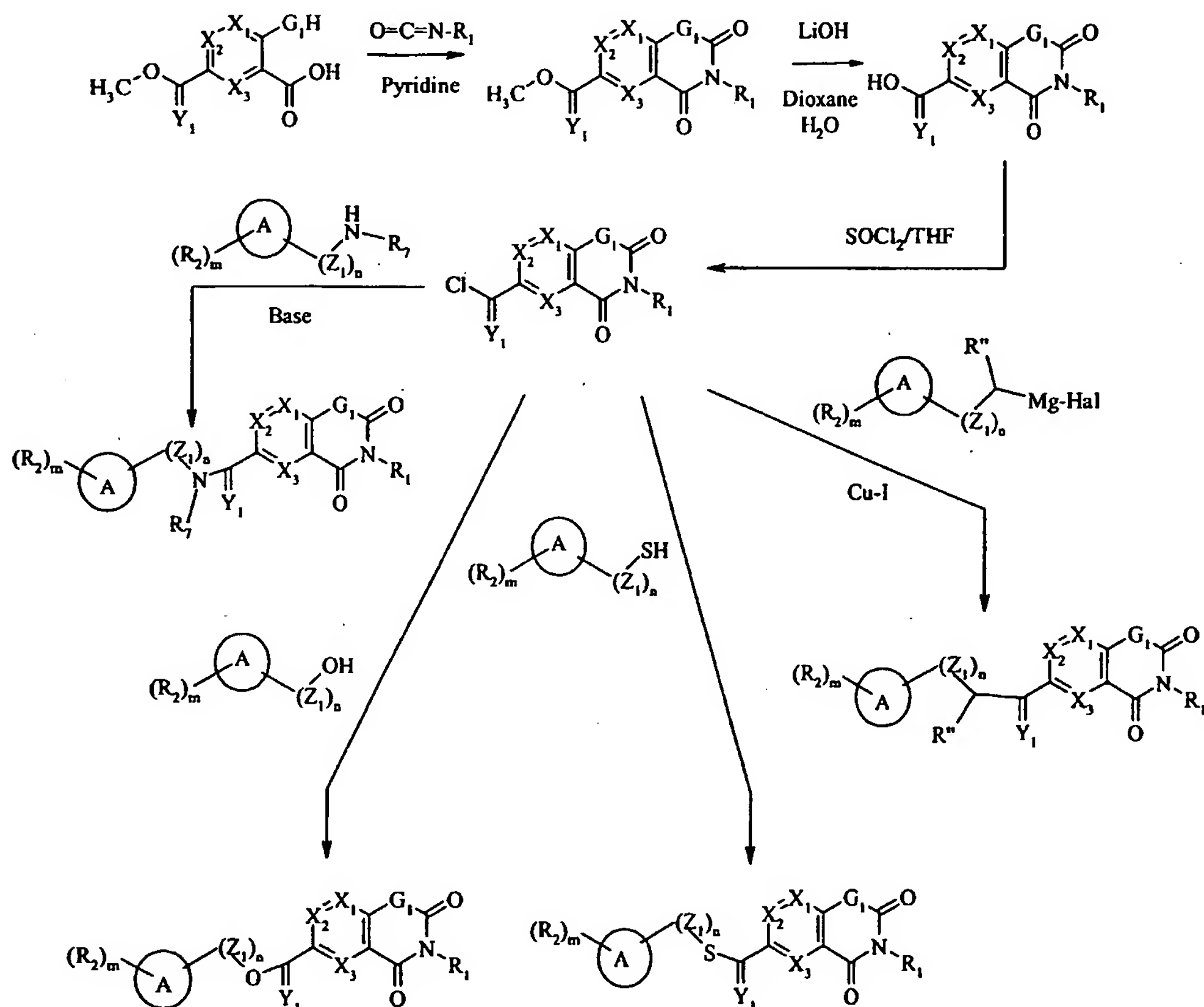


in which X_1 , X_2 , X_3 , G_1 , Z_1 , R_1 , R_2 , A , n and m are as defined hereinbefore,

compounds of formula (I/b) constitute some compounds of the invention, which are purified, where appropriate, according to a conventional purification technique, which are separated, where appropriate, into their different isomers according to a conventional

separation technique, and which are converted, where appropriate, into addition salts thereof with a pharmaceutically-acceptable acid or base, or into N-oxide thereof.

A general process for the synthesis of the compounds of formula (I) is described in the following scheme:



- 5 in which R_7 is hydrogen or $(C_1-C_6)alkyl$, R'' is hydrogen or $(C_1-C_6)alkyl$, and $R_1, R_2, G_1, X_1, X_2, X_3, A, Y_1, Z_1, n$ and m have the same meaning as that defined for the compound of formula (I).

The compounds of the invention that are present in the form of a mixture of diastereoisomers are isolated in a pure form by using conventional separation techniques such as chromatography.

As mentioned above, compounds of formula (I) of the present invention are matrix metalloprotease inhibitors, and more particularly inhibitors of the enzyme MMP-13.

In this respect, their use is recommended for the treatment of diseases or complaints involving a therapy by MMP-13 inhibition. By way of example, the use of the compounds of the present invention may be recommended for the treatment of any pathology in which destruction of extracellular matrix tissue occurs, and most particularly pathologies such as arthritis, rheumatoid arthritis, osteoarthritis, osteoporosis, periodontal diseases, inflammatory bowel disease, psoriasis, multiple sclerosis, cardiac insufficiency, atherosclerosis, asthma, chronic obstructive pulmonary disease, age-related macular degeneration and cancers.

The present invention also relates to pharmaceutical compositions comprising as active ingredient at least one compound of formula (I), an isomer thereof, a N-oxide thereof, or an addition salt thereof with a pharmaceutically-acceptable acid or base, alone or in combination with one or more pharmaceutically-acceptable, inert, non-toxic excipients or carriers.

Among the pharmaceutical compositions according to the invention, there may be mentioned more especially those that are suitable for oral, parenteral (intravenous, intramuscular or subcutaneous), per- or trans-cutaneous, intravaginal, rectal, nasal, perlingual, buccal, ocular or respiratory administration.

Pharmaceutical compositions according to the invention for parenteral injections especially include aqueous and non-aqueous sterile solutions, dispersions, suspension and emulsions, and also sterile powders for reconstituting injectable solutions or dispersions.

Pharmaceutical compositions according to the invention for oral administration in solid form especially include tablets or dragées, sublingual tablets, sachets, gelatin capsules and granules, for oral, nasal, buccal or ocular administration in liquid form, especially include emulsions, solutions, suspensions, drop, syrups and aerosols.

Pharmaceutical compositions for rectal or vaginal administration are preferably suppositories, and those for per- or trans-cutaneous administration especially include powders, aerosols, creams, ointment, gels and patches.

5 The pharmaceutical compositions mentioned hereinbefore illustrate the invention but do not limit it in any way.

Among the pharmaceutically acceptable, inert, non-toxic excipients or carriers there may be mentioned, by way of non-limiting example, diluents, solvents, preservatives, wetting agents, emulsifiers, dispersing agents, binders, swelling agents, disintegrating agents, retardants, lubricants, absorbents, suspending agents, colorants, aromatizing agents etc...

0 The useful dosage varies according to the age and weight of the patient, the administration route, the pharmaceutical composition used, the nature and severity of the disorder and the administration of any associated treatments. The dosage ranges from 2 mg to 1 g per day in one or more administrations. The compositions are prepared by methods that are common to those skilled in the art and generally comprise 0.5% to 60% by weight of active
5 principle (compound of formula (I)) and 40% to 99.5% by weight of pharmaceutically acceptable excipients or carriers.

The examples that follow illustrate the invention but do not limit it in any way.

The starting materials used are products that are known or that are prepared according to known operating procedures. The various preparations yield synthetic intermediates that
10 are useful in preparation of the compounds of the invention. Some of these intermediates are new compounds.

The structures of the compounds described in the Examples and Preparations were determined according to the usual spectrophotometric techniques (infrared, nuclear magnetic resonance, mass spectrometry, ...)

15 In the Examples, it is understood that :

- DMSO means dimethylsulfoxide,
- TOTU means O-(ethoxycarbonyl)cyanomethylamino]-*N-N-N'-N'*-tetramethyluronium fluoroborate,

EXAMPLES

5 Intermediate A : 3-benzyl-6-bromo-3,4-dihydro-benzothiazine-2,4-dione

A stirred suspension of 5-bromo-2-mercaptobenzoic acid (prepared after K. Sindelar and coll., Coll. Czech. Chem. Comm., 1988, 53 (2), 340) (8 g, 34.3 mmol) in pyridine (100 ml) was treated with benzyl isocyanate (4.3 ml, 34.3 mmol) and the mixture was heated at 105°C for 7 hours under a nitrogen atmosphere. Further benzyl isocyanate was added (4.3
0 ml) and the mixture heated at 105°C overnight under stirring. After cooling to room temperature, water was added until precipitation and the suspension stirred for 1 hour. The resulting precipitate was collected by filtration, washed several times with water and dried under high vacuum to give 11.5g (yield : 96%) of the entitled compound as a white amorphous solid.

5 Intermediate B : 3-benzyl-6-cyano-3,4-dihydro-benzothiazine-2,4-dione

CuCN (0.197g, 2.2 mmol) was added to a suspension of 3-benzyl-6-bromo-3,4-dihydro-benzothiazine-2,4-dione (intermediate A ; 0.35 g, 1.22 mmol) in N-methylpyrrolidone (4 ml) and the suspension obtained was heated at reflux under stirring for 2.5 hours. The solvent was removed under reduced pressure and the sticky residue obtained was stirred in
10 a mixture of NH₄OH solution and dichloromethane. The organic phase was separated, washed with brine and dried over Na₂SO₄. The solvent was evaporated to afford 0.28 g of crude solid that was purified by chromatography on silica gel (cyclohexane 20/CH₂Cl₂ 80) to give the entitled compound (0.15 g ; yield : 51%) as a white solid pure in TLC (cyclohexane 20 / CH₂Cl₂ 80 ; R_f = 0.40).

15 Intermediate C : 3-benzyl-6-carboxy-3,4-dihydro-benzothiazine-2,4-dione

A suspension of 3-benzyl-6-cyano-3,4-dihydro-benzothiazine-2,4-dione (intermediate B ; 0.12 g, 0.4 mmol) in concentrated sulfuric acid (3 ml) and water (3 ml) was heated at reflux under stirring for 3 hours. After cooling to room temperature, water was added and the insoluble solid was collected by filtration, washed several times with water and dried under high vacuum to give, after purification by chromatography on silica gel (CH₂Cl₂ 95/methanol 5), 0.04g (yield : 31%) of the entitled compound as a white solid pure in TLC (CH₂Cl₂ 90 / methanol 10 ; R_f = 0.30).

Intermediate D : 4-hydroxy-N,N'-bis[(4-methoxyphenyl)methyl]-1,3-benzenedicarboxamide

A mixture of 4-hydroxyisophthalic acid (2.0 g ; 11 mmol) in thionyl chloride (20 ml) and dimethylformamide (2 drops) was heated at reflux under stirring overnight. The excess of thionyl chloride was removed by evaporation and the residue dissolved into dichloromethane (100 ml).

After cooling, 4-methoxybenzylamine (6.8 g ; 50 mmol) was added in one portion and the mixture obtained was stirred at room temperature for 1 hour. The insoluble solid was separated by filtration and purified by chromatography on silica gel (CH₂Cl₂ 95/methanol 5) to give 2.0 g of the entitled compound (yield : 43%) as a white solid pure in TLC (CH₂Cl₂ 90/methanol 10 ; R_f = 0.70).

Intermediate E : 6-bromo-3,4-dihydro-benzothiazine-2,4-dione

Under an inert atmosphere, aluminium chloride (5.51 g, 41.3 mmol) was added in portions to a suspension of 3-benzyl-6-bromo-3,4-dihydro-benzothiazine-2,4-dione (intermediate A ; 2.4 g, 6.89 mmol) in benzene (50 ml) and the mixture obtained was heated at 50°C under stirring for 2 hours. After cooling, the mixture was poured into iced water, the precipitated product was filtrated after 1 h standing, washed several times with water until neutral pH, dried and finally triturated in dichloromethane then dried under high vacuum to give 1.5 g (yield : 84%) of the entitled compound pure in TLC (CH₂Cl₂ ; R_f = 0.10).

NMR H¹ (DMSO) δ (ppm) : 5.5(s, 2H); 7.25-7.35 (m, 3H); 7.5 (m, 1H); 7.65 (m, 2H); 8.65 (m, 1H); 8.75 (m, 1H); 9.05 (s, 1H).

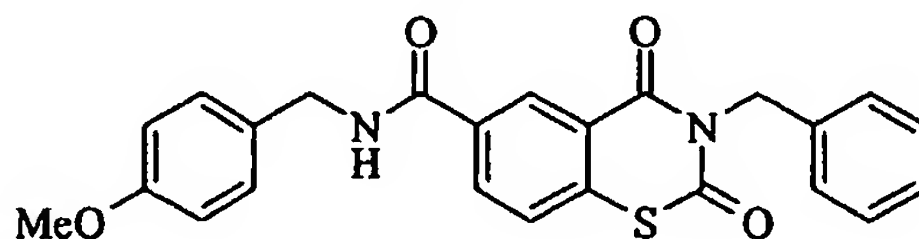
Intermediate F : t-butyl 4-(6-bromo-2,4-dioxo-4H-1,3-benzothiazin-3-ylmethyl)-benzoate

A suspension of 6-bromo-3,4-dihydro-benzothiazine-2,4-dione (intermediate E ; 1.5 g, 5.8 mmol) and cesium carbonate (1.89 g, 5.8 mmol) in dimethylformamide (20 ml) was stirred under a nitrogen atmosphere for 0.5 hour at room temperature and treated with 4-(t-butoxycarbonyl)benzyl bromide (1.57 g, 5.8 mmol) ; the mixture obtained was heated at 80°C under stirring and inert atmosphere for 2 hours. The solvent was removed under reduced pressure, and the residue was partitioned between water and dichloromethane. The aqueous layer was reextracted with CH₂Cl₂, the organic phases combined and dried over Na₂SO₄. The solvent was removed under reduced pressure to afford 2.4 g of crude solid that was purified by chromatography on silica gel (CH₂Cl₂) to give the entitled compound (1.95 g ; yield : 85%) as a white solid pure in TLC (CH₂Cl₂ 99/CH₃OH 1 ; R_f = 0.70).

Intermediate G : 4-(6-bromo-2,4-dioxo-4H-1,3-benzothiazin-3-ylmethyl)-benzoic acid

A stirred solution of 6-bromo-3-(4-t-butoxycarbonylbenzyl)-3,4-dihydro-benzothiazine-2,4-dione (intermediate F ; 0.6 g, 1.34 mmol) in CH₂Cl₂ (60 ml) was treated at room temperature with trifluoroacetic acid (6 ml). The reaction mixture was stirred overnight at room temperature and poured into water; the resulting insoluble product was isolated by filtration, washed several times until neutral pH and dried under vacuum to afford the entitled acid (0.45 g ; yield : 86%) as a white solid pure in TLC (CH₂Cl₂ 95/CH₃OH 5 ; R_f = 0.35).

Example 1 : 3-Benzyl-2,4-dioxo-3,4-dihydro-2H-benzo[e][1,3]thiazine-6-carboxylic acid 4-methoxy benzylamide



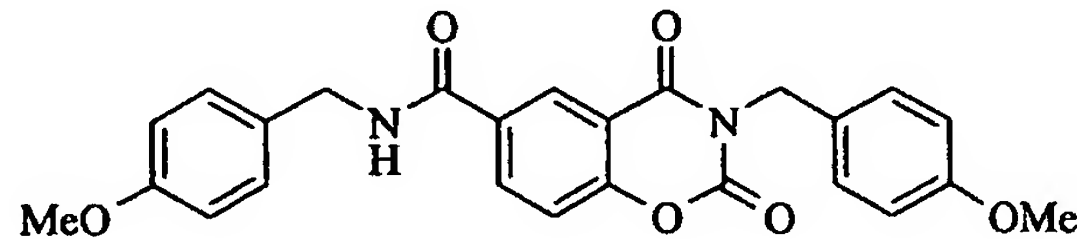
To a solution of 25 mg (0.08 mmol) of intermediate C in 2 ml of dimethylformamide, 10.9 mg (0.08 mmol) of 4-methoxybenzylamine and 26 mg (0.08 mmol) of TOTU were added under stirring. After external cooling with ice bath, 20 mg (0.16 mmol) of N,N-diisopropyl-N-ethylamine were added and the yellow resulting solution was stirred overnight at room temperature. The solvent was removed under vacuum and the residual brown oil was purified by column chromatography over silica gel (dichloromethane then dichloromethane / methanol : 99.5 / 0.5) to yield 13 mg of the desired product (yield : 38%).

N.M.R (CDCl₃) ¹H δ (ppm) : 3.8 (s, 3H) ; 4.6 (d, 2H) ; 5.35 (s, 2H) ; 6.5 (s, 1H) ; 6.9 (d, 2H) ; 7.2-7.35 (m, 5H) ; 7.4 (d, 2H) ; 7.5 (d, 2H) ; 8.15 (d, 1H) ; 8.6 (s, 1H).

IR : 1649, 1543, 1514, 1406, 1284, 1253, 1231, 1185, 1145, 1030, 824, 731 cm⁻¹

HPLC : Purity = 96%

Example 2 : 3-Benzyl-2,4-dioxo-3,4-dihydro-2H-benzo[e][1,3]oxazine-6-carboxylic acid 4-methoxy benzylamide



A cooled solution of N, N'-bis-(4-methoxybenzyl)-4-hydroxyisophthalic acid (intermediate D, 0.42 g, 1 mmol) in pyridine (5 ml) and acetonitrile (3 ml) was treated with ethyl chloroformate (0.12 g, 1.1 mmol) under stirring and the mixture was heated at 120°C for 8 hours under a nitrogen atmosphere. Further ethyl chloroformate was added (1.1 ml) and the mixture heated at 120°C overnight under stirring. After cooling to room temperature, the reaction mixture was poured into diluted hydrochloric solution and the product extracted several times with dichloromethane. The joined organic phases were washed with diluted hydrochloric solution, diluted solution of sodium hydroxide and brine successively and dried over Na₂SO₄. The solvent was evaporated and the residue triturated in dichloromethane; the insoluble solid is filtrated and dried to afford the entitled compound (0.32 g ; yield : 71%) as a white solid pure in TLC (CH₂Cl₂ 95/methanol ; R_f = 0.40).

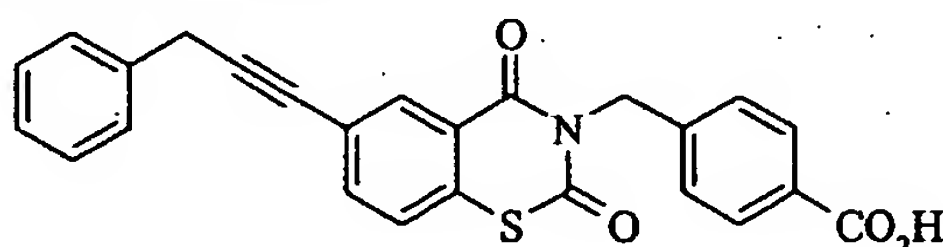
N.M.R (DMSO-*d*₆) ¹H δ (ppm) : 3.7 (s, 6H); 4.4 (d, 2H); 6.8-6.9 (m, 4H); 7.25 (d, 2H); 7.3 (d, 2H); 7.5 (d, 1H); 8.25 (d, 1H); 8.5 (s, 1H); 9.25 (t, 1H).

IR : 1759, 1693, 1638, 1513, 1446, 1327, 1305, 1244 cm^{-1}

MP = 157°C

HPLC : Purity = 98.5%

Example 3 : 4-[2,4-Dioxo-6-(3-phenyl-prop-1-ynyl)-4H-1,3-benzothiazin-3-ylmethyl]-benzoic acid



6-bromo-3-(4-carboxybenzyl)-3,4-dihydro-benzothiazine-2,4-dione (Intermediate G) (0.39 g; 0.994 mmol) in dimethylformamide (4 ml) was stirred at room temperature under nitrogen atmosphere and N-ethyl-N,N-diisopropylamine (0.51 g, 3.97 mmol) was added ; the mixture was stirred until complete solubilisation. At this time, 3-phenylprop-1-yne (0.16 g; 1.39 mmol) was added followed by $\text{PdCl}_2(\text{PPh}_3)_2$ (30 mg) and a catalytic amount of CuI. The mixture obtained was heated to 50°C under nitrogen atmosphere and maintained under stirring for 3 hours. After cooling, the solvent was removed under reduced pressure and the semi-solid residue obtained was stirred in a mixture of water and dichloromethane for 25 minutes. The solid insoluble in the 2 phases was isolated by filtration, washed with CH_2Cl_2 and dried under vacuum to afford a first portion (0.16 g) of the entitled compound. The organic phase was separated, washed with brine, dried over Na_2SO_4 and evaporated to give an additional portion (0.23 g) of the desired compound (yield 92%).

N.M.R ($\text{DMSO}-d_6$) ^1H δ (ppm) : 3.94 (s, 2H); 5.23 (s, 2H); 7.27 (t, 1H); 7.37 (t, 2H); 7.40-7.50 (m, 4H); 7.67 (d, 1H); 7.84-7.95 (m, 2H); 8.23 (s, 1H); 12.75-13.05 (m, 1H).

IR : 1690, 1638, 1425, 1408, 1341, 1318, 1297, 1286, 1181, 1149, 913, 768, 726, 707 cm^{-1}

MP = 240-242°C

HPLC : Purity = 98%

PHARMACOLOGICAL STUDIES OF COMPOUNDS OF THE INVENTION

Example 4 : Evaluation of the in vitro activity of the MMP-13 inhibitor compounds according to the invention.

The inhibitory activity of the compounds of formula (I) according to the invention with respect to matrix metalloprotease-13 is evaluated by testing the ability of the compounds of the invention to inhibit the proteolysis of a peptide substrate with MMP-13.

The peptide substrate used in the test is the following peptide: Ac-Pro-Leu-Gly-thioester-Leu-Leu-Gly-OEt.

The inhibitory activity of a compound of formula (I) according to the invention is expressed as the IC_{50} value, which is the concentration of inhibitor for which an inhibition of 50% of the activity of the matrix metalloprotease under consideration is observed.

To carry out this test, a reaction medium of 100 μ l volume is prepared, containing: 50 mM of HEPES buffer, 10 mM of $CaCl_2$ and 1 mM of 5,5'-dithiobis-(2-nitrobenzoic acid) (DTNB), and 100 μ M of substrate, the pH being adjusted to 7.0.

Increasing concentrations of the inhibitory compound present in a 2.0% DMSO solution and 2.5 nM of the catalytic domain of human MMP-13 are added to the test samples.

The concentrations of inhibitors present in the test samples range from 100 μ M to 0.5 nM.

The measurement of the proteolysis of the substrate peptide is monitored by measuring the absorbance at 405 nm using a spectrophotometer for reading microplates, at the laboratory temperature, the measurements being carried out continuously for 10 to 15 minutes.

The IC_{50} values are calculated from a curve in which the percentage of the catalytic activity relative to the control is represented on the X-axis and the concentration of inhibitor is represented on the Y-axis.

The IC_{50} values on MMP-13 of the compounds of Examples 1, 2 and 3 are respectively 0.037 μ M, 0.063 μ M, and 0.0012 μ M.

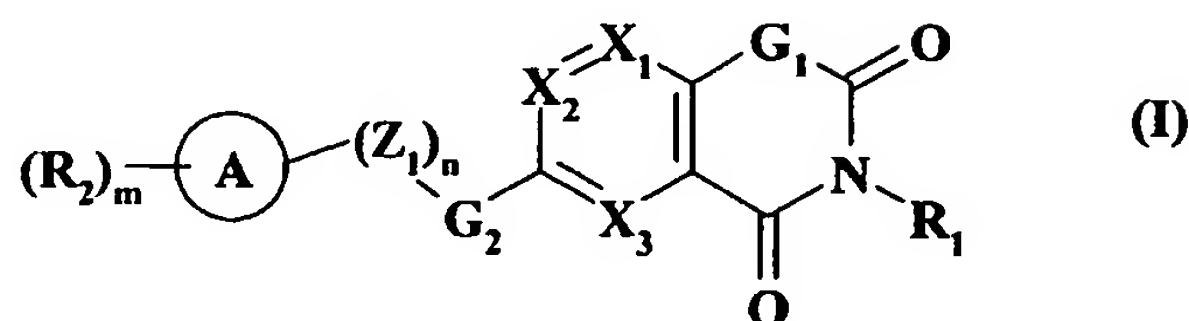
The test described above for the inhibition of MMP-13 was also adapted and used to determine the ability of the compounds of formula (I) to inhibit the matrix metalloproteases MMP-1, MMP-2, MMP-3, MMP-7, MMP-9, MMP-12 and MMP-14.

The results obtained show that the compounds according to the invention generally have IC_{50} values for MMP-13 which are about 100 times lower than the IC_{50} values for the same compounds with respect to the other matrix metalloproteases tested. Then the IC_{50} values

on MMP-1, MMP-2, MMP-3, MMP-7, MMP-9, MMP-12 and MMP-14 for the compound of Example 1 are respectively 30 μ M, 100 μ M, 18 μ M, 30 μ M, 100 μ M, 100 μ M, and 100 μ M.

CLAIMS

1- A compound selected from those of formula (I):



wherein:

- 5 • X_1 , X_2 , and X_3 , independently of each other, represent a nitrogen atom or a group $-CR_3$ in which R_3 represents a group selected from hydrogen, (C_1-C_6) alkyl, amino, mono (C_1-C_6) alkylamino, di (C_1-C_6) alkylamino, hydroxy, (C_1-C_6) alkoxy, and halogen, it being understood that not more than two of the groups X_1 , X_2 and X_3 simultaneously represent a nitrogen atom,
- 0 • G_1 represents an oxygen atom or a group $S(O)_p$ in which p represents an integer from 0 to 2 inclusive,
- G_2 represents a group selected from carbon-carbon triple bond, $C=O$, $C=S$, $S(O)_q$ in which q represents an integer from 0 to 2 inclusive, or a group of formula (i/a):



- 5 in which the carbon atom with the number 1 is attached to the bicycle of the compound of formula (I), Y_1 represents a group selected from oxygen, sulphur, $-NH$ and $-N(C_1-C_6)$ alkyl, and Y_2 represents a group selected from oxygen, sulphur, $-NH$ and $-N(C_1-C_6)$ alkyl,
- n represents an integer from 0 to 6 inclusive,
- Z_1 represents $-CR_4R_5$, wherein R_4 and R_5 , identical or different independently of each other, represent a group selected from hydrogen, (C_1-C_6) alkyl, trihalogeno (C_1-C_6) alkyl, halogen, amino, mono (C_1-C_6) alkylamino, di (C_1-C_6) alkylamino in which each alkyl moiety
- 0

is identical or different, $-OR_6$, $-SR_6$, and $-C(=O)OR_6$, in which R_6 is hydrogen atom or (C_1-C_6) alkyl, and

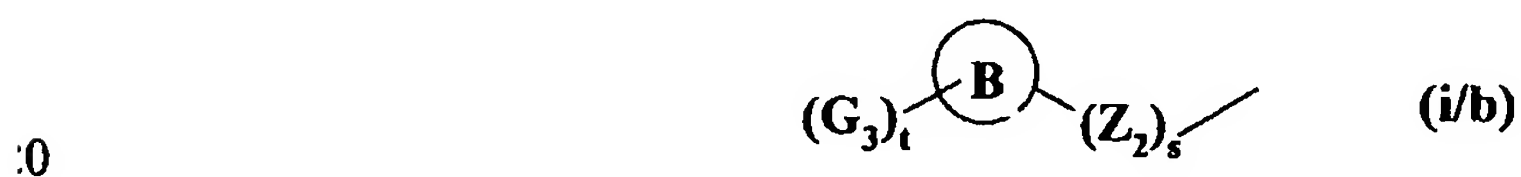
- wherein when n is greater than or equal to 2, the hydrocarbon chain Z_1 optionally contains one to two isolated or conjugated multiple bonds,

5 - and/or wherein when n is greater than or equal to 2 one of said $-CR_4R_5$ may be replaced with a group selected from oxygen, $S(O)_r$ in which r represents an integer from 0 to 2 inclusive, $-NH$ and $-N(C_1-C_6)$ alkyl,

• A represents a group selected from aryl, heteroaryl, cycloalkyl, and heterocycloalkyl, these groups being a 5- or 6-membered monocycle, or bicycle itself composed of two 5- or
0 6-membered monocycles,

• R_1 represents a group selected from :

- hydrogen,
- (C_1-C_6) alkyl, (C_2-C_6) alkenyl, (C_2-C_6) alkynyl, these groups may be optionally substituted with one or more groups, which may be identical or different
5 independently of each other, selected from amino, cyano, trihalogeno (C_1-C_6) alkyl, cycloalkyl, $-C(=O)NR_7R_8$, $-C(=O)OR_7$, OR_7 , and SR_7 , in which R_7 and R_8 , which may be identical or different independently of each other, represent hydrogen or (C_1-C_6) alkyl,
- and the group of formula (i/b) :



✓ in which s is an integer from 0 to 8 inclusive,

✓ Z_2 represents $-CR_9R_{10}$ wherein R_9 and R_{10} , identical or different independently of each other, represent a group selected from hydrogen, (C_1-C_6) alkyl, phenyl, trihalogeno (C_1-C_6) alkyl, halogen, amino, OR_6 , SR_6 and $-C(=O)OR_6$ in which R_6 is
5 as defined hereinbefore, and

- wherein when s is greater than or equal to 2, the hydrocarbon chain Z_2 optionally contains one or two isolated or conjugated multiple bonds,

- and/or wherein when p is greater or equal to 2, one of said $-CR_9R_{10}$ may be replaced with a group selected from oxygen, $S(O)_u$ in which u is an integer from 0 to 2 inclusive, $-NH$, $-N(C_1-C_6)alkyl$, and carbonyl,

✓ B represents a group selected from aryl, heteroaryl, cycloalkyl, and heterocycloalkyl, these groups being a 5- or 6-membered monocycle, or bicycle itself composed of two 5- or 6-membered monocycles,

✓ t is an integer from 0 to 7 inclusive,

✓ the group(s) G_3 , which may be identical or different independently of each other, is (are) selected from $(C_1-C_6)alkyl$, halogen, CN , NO_2 , CF_3 , OCF_3 , $-(CH_2)_kNR_{11}R_{12}$, $-N(R_{11})C(=O)R_{12}$, $-N(R_{11})C(=O)OR_{12}$, $-N(R_{11})SO_2R_{12}$, $-N(SO_2R_{11})_2$, $-OR_{11}$, $-S(O)_{k1}R_{11}$, $-SO_2-N(R_{11})-(CH_2)_{k2}-NR_{12}R_{13}$, $-(CH_2)_kSO_2NR_{11}R_{12}$, $-X_4(CH_2)_kC(=O)OR_{11}$, $-(CH_2)_kC(=O)OR_{11}$, $-C(=O)O-(CH_2)_{k2}-NR_{11}R_{12}$, $-C(=O)O-(CH_2)_{k2}-C(=O)OR_{14}$, $-X_4(CH_2)_kC(=O)NR_{11}R_{12}$, $-(CH_2)_kC(=O)NR_{11}R_{12}$, $-R_{15}-C(=O)OR_{11}$, $-X_5-R_{16}$, and $-C(=O)-R_{17}-NR_{11}R_{12}$ in which :

- X_4 represents a group selected from oxygen, sulphur optionally substituted by one or two oxygen, and nitrogen substituted by a hydrogen or a $(C_1-C_6)alkyl$ group,

- k is an integer from 0 to 3 inclusive,

- $k1$ is an integer from 0 to 2 inclusive,

- $k2$ is an integer from 1 to 4 inclusive,

- R_{11} , R_{12} and R_{13} , which may be identical or different independently of each other, are selected from hydrogen and $(C_1-C_6)alkyl$,

- R_{14} represents a group selected from $(C_1-C_6)alkyl$, $-R_{17}-NR_{11}R_{12}$, $-R_{17}-NR_{11}-C(=O)-R_{17}-NR_{12}R_{13}$, and $-C(=O)O-R_{17}-NR_{11}R_{12}$ in which R_{17} represents a

a linear or branched (C₁-C₆)alkylene group, and R₁₁, R₁₂ and R₁₃ are as defined hereinbefore,

- R₁₅ represents a (C₃-C₆)cycloalkyl group,
- X₅ represents a group selected from a single bond, -CH₂-, oxygen, sulphur optionally substituted by one or two oxygen, and nitrogen substituted by hydrogen or (C₁-C₆)alkyl,
- R₁₆ represents a group selected from :
 - o a 5- or 6-membered monocyclic aryl or heteroaryl, which is optionally substituted by one or more groups, which may be identical or different independently of each other, selected from (C₁-C₆)alkyl, halogen, hydroxy, cyano, tetrazolyl, amino, and -C(=O)OR₇ wherein R₇ represents hydrogen or (C₁-C₆)alkyl,
 - o and a 5- or 6-membered monocyclic cycloalkyl or heterocycloalkyl, which is optionally substituted by one or more groups, which may be identical or different independently of each other, selected from (C₁-C₆)alkyl, halogen, hydroxy, oxo, cyano, tetrazolyl, amino, and -C(=O)OR₇ wherein R₇ represents hydrogen or (C₁-C₆)alkyl,
- m is an integer from 0 to 7 inclusive,
- the group(s) R₂, which may be identical or different independently of each other, is (are) selected from (C₁-C₆)alkyl, halogen, -CN, -NO₂, -SCF₃, -CF₃, -OCF₃, -NR₇R₈, -OR₇, -SR₇, -SOR₇, -SO₂R₇, -(CH₂)_kSO₂NR₇R₈, -X₇(CH₂)_kC(=O)OR₇, -(CH₂)_kC(=O)OR₇, -X₇(CH₂)_kC(=O)NR₇R₈, -(CH₂)_kC(=O)NR₇R₈, and -X₈-R₁₈ in which:
 - X₇ represents a group selected from oxygen, sulphur optionally substituted by one or two oxygen, and nitrogen substituted by hydrogen or (C₁-C₆)alkyl,
 - k is an integer from 0 to 3 inclusive,
 - R₇ and R₈, which may be identical or different independently of each other, are selected from hydrogen and (C₁-C₆)alkyl,

- X_8 represents a group selected from single bond, $-CH_2-$, oxygen, sulphur optionally substituted by one or two oxygen, and nitrogen substituted by hydrogen or (C_1-C_6) alkyl,
- R_{18} represents a group selected from phenyl, a 5- or 6-membered monocyclic, heteroaryl, and a 5- or 6-membered monocyclic cycloalkyl, each of these groups being optionally substituted by one or more groups, which may be identical or different independently of each other, selected from (C_1-C_6) alkyl, halogen, hydroxy and amino,

and optionally, its racemic forms, isomers, N-oxides, and pharmaceutically acceptable salts,

it being understood that :

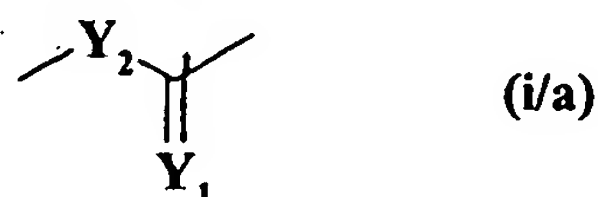
- an aryl group denotes an aromatic monocyclic or bicyclic system containing from 5 to 10 carbon atoms, and in the case of a bicyclic system, one of the ring of which is aromatic in character, and the other ring of which may be aromatic or partially hydrogenated ;
- a heteroaryl group denotes an aryl group as described above in which 1 to 4 carbon atoms are replaced by 1 to 4 hetero atoms selected from oxygen, sulfur and nitrogen ;
- a cycloalkyl group denotes a monocyclic or bicyclic system containing from 3 to 10 carbon atoms, these systems being saturated or partially unsaturated but without aromatic character ;
- a heterocycloalkyl group denotes a cycloalkyl group as defined hereinbefore in which 1 to 4 carbon atoms are replaced by 1 to 4 hetero atoms selected from oxygen, sulfur, and nitrogen,
- and a bicycle denotes two fused-monocycle;

and with the proviso that the compound of formula (I) is not 6-(2,4-dioxo-3,4-dihydro-2H-1,3-benzothiazine)-benzoate, 6-phenylthio-2,4-dioxo-3,4-dihydro-2H-1,3-benzothiazine, 6-benzylsulphonyl-2,4-dioxo-3,4-dihydro-2H-1,3-benzothiazine, 6-benzophenone-2,4-dioxo-

3,4-dihydro-2H-1,3-benzothiazine and 6-(2,4-dihydroxy)-benzophenone-2,4-dioxo-3,4-dihydro-2H-1,3-benzothiazine.

2- A compound according to claim 1 wherein :

- G_1 represents a sulphur atom,
- 5 • G_2 represents a group of formula (i/a):

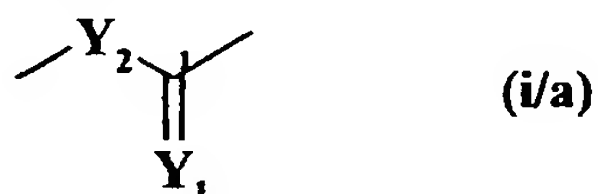


in which the carbon atom with the number 1 is attached to the bicycle of the compound of formula (I), Y_1 represents an oxygen atom, and Y_2 represents a group -NH,

- $X_1, X_2, X_3, n, Z_1, A, R_1, m$ and R_2 are as defined in formula (I),
- 0 and optionally, its racemic forms, isomers, N-oxides, and pharmaceutically acceptable salts.

3- A compound according to claim 1 wherein :

- G_1 represents an oxygen atom,
- G_2 represents a group of formula (i/a):



- 5 in which the carbon atom with the number 1 is attached to the bicycle of the compound of formula (I), Y_1 represents an oxygen atom, and Y_2 represents a group -NH,

- $X_1, X_2, X_3, n, Z_1, A, R_1, m$ and R_2 are as defined in formula (I),
- 0 and optionally, its racemic forms, isomers, N-oxides, and pharmaceutically acceptable salts.

4- A compound according to claim 1 wherein :

- G_1 represents a sulphur atom,
- G_2 represents a carbon-carbon triple bond,
- n represents an integer from 1 to 6 inclusive,
- 5 $X_1, X_2, X_3, Z_1, A, R_1, m$ and R_2 are as defined in formula (I),

and optionally, its racemic forms, isomers, N-oxides, and pharmaceutically acceptable salts.

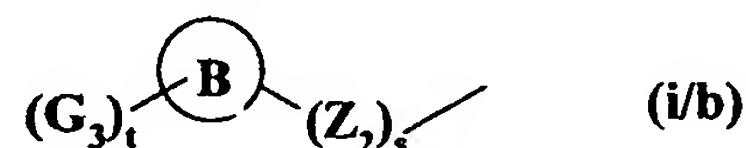
5- A compound according to claim 1 wherein :

- G_1 represents an oxygen atom,
- 5 • G_2 represents a carbon-carbon triple bond,
- n represents an integer from 1 to 6 inclusive,

X_1 , X_2 , X_3 , Z_1 , A , R_1 , m and R_2 are as defined in formula (I),

and optionally, its racemic forms, isomers, N-oxides, and pharmaceutically acceptable salts.

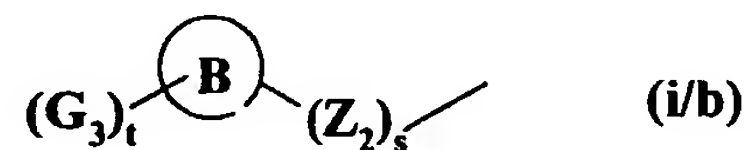
- 0 6- A compound according to claim 1 wherein R_1 represents a group of formula (i/b):



wherein Z_2 , s , B , G_3 and t are as defined in the compound of formula (I),

and optionally, its racemic forms, isomers, N-oxides, and pharmaceutically acceptable salts.

- 5 7- A compound according to claim 6 wherein R_1 represents a group of formula (i/b):

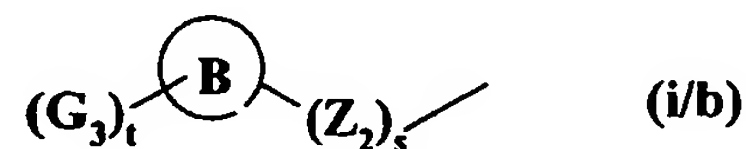


wherein Z_2 represents a group $-\text{CR}_9\text{R}_{10}$ in which R_9 and R_{10} represents each a hydrogen atom, s is equal to one, and B , G_3 , and t are as defined in the compound of formula (I),

and optionally, its racemic forms, isomers, N-oxides, and pharmaceutically acceptable salts.

0

- 8- A compound according to claim 7 wherein R_1 represents a group of formula (i/b):



wherein B represents a phenyl group, t is equal to 0 or 1, and G_3 , when it is present, represents a group selected from OR_{11} , halogen, and $(\text{CH}_2)_k\text{C}(=\text{O})\text{OR}_{11}$ in which R_{11} represents an hydrogen atom or a $(\text{C}_1\text{-C}_6)$ alkyl group and k is equal to zero,

5

and optionally, its racemic forms, isomers, N-oxides, and pharmaceutically acceptable salts.

9- A compound according to claim 1 wherein X_1 , X_2 , and X_3 represent each a group $-CR_3$ in which R_3 represents a hydrogen atom, its racemic forms, isomers, N-oxides, and pharmaceutically acceptable salts.

10- A compound according to claim 1 wherein X_1 represents a group $-CR_3$ in which R_3 represents a hydrogen atom, X_2 represents a nitrogen atom or a group $-CR_3$ in which R_3 represents a hydrogen atom, and X_3 represents a group $-CR_3$ in which R_3 represents a hydrogen atom, and optionally, its racemic forms, isomers, N-oxides, and pharmaceutically acceptable salts.

11- A compound according to claim 1 wherein Z_1 represents $-CR_4R_5$ in which R_4 and R_5 represent each a hydrogen atom, and n is equal to one, and optionally, its racemic forms, isomers, N-oxides, and pharmaceutically acceptable salts.

12- A compound according to claim 1 wherein A represents a phenyl group, m is equal to zero or one, and R_2 represents a (C_1-C_6) alkoxy group or a hydrogen atom, and optionally, its racemic forms, isomers, N-oxides, and pharmaceutically acceptable salts.

13- A compound according to claim 1 wherein A represents a pyridyl group, m is equal to zero or one, and R_2 represents a (C_1-C_6) alkoxy group or a hydrogen atom, and optionally, its racemic forms, isomers, N-oxides, and pharmaceutically acceptable salts.

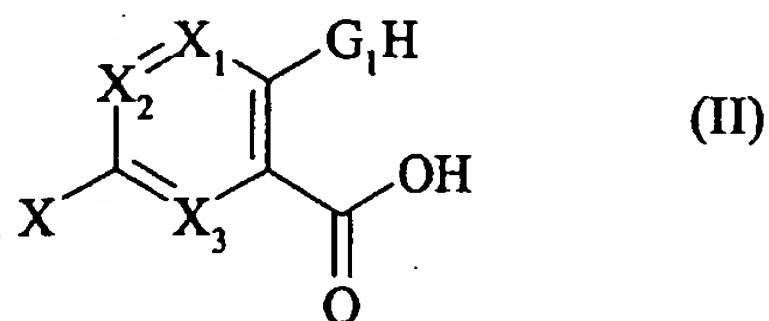
14- A compound according to claim 1 wherein A represents an imidazolyl group, optionally, its racemic forms, isomers, N-oxides, and pharmaceutically acceptable salts.

15- A compound according to claim 1 selected from:

- 3-benzyl-2,4-dioxo-3,4-dihydro-2*H*-benzo[*e*][1,3]thiazine-6-carboxylic acid 4-methoxy benzylamide;

- 3-(4-methoxybenzyl)2,4-dioxo-3,4-dihydro-2*H*-benzo[*e*][1,3]oxazine-6-carboxylic acid 4-methoxybenzylamide;
- and 4-[2,4-dioxo-6-(3-phenyl-prop-1-ynyl)-4*H*-1,3-benzothiazin-3-ylmethyl]-benzoic acid.

5 16- A process for the preparation of compounds according to claim 1 in which uses as starting material a compound of formula (II):



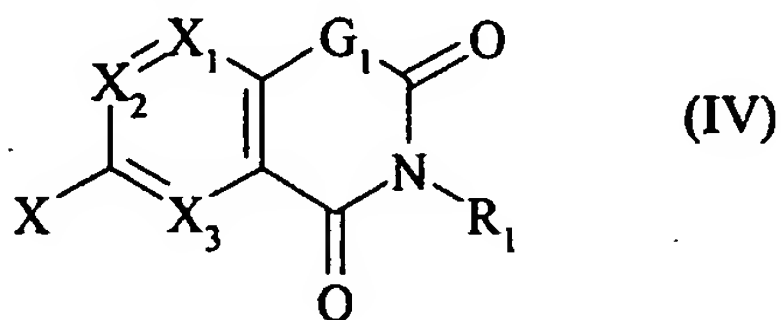
in which X_1 , X_2 , X_3 , and G_1 have the same definitions as the compound of formula (I), and X represents a leaving group selected from halogen, triflate, mesylate, tosylate and SO_2 alkyl,

compound of formula (II) which is treated in basic medium with an isocyanate compound of formula (III):



in which R_1 has the same definitions as the compound of formula (I),

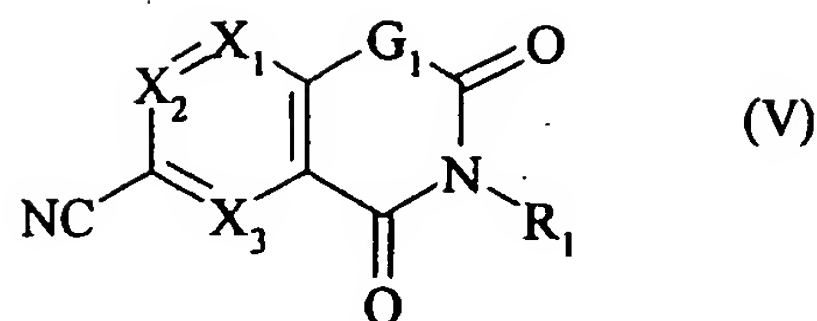
5 to yield the compound of formula (IV) :



in which X_1 , X_2 , X_3 , G_1 , X , and R_1 are as defined hereinbefore,

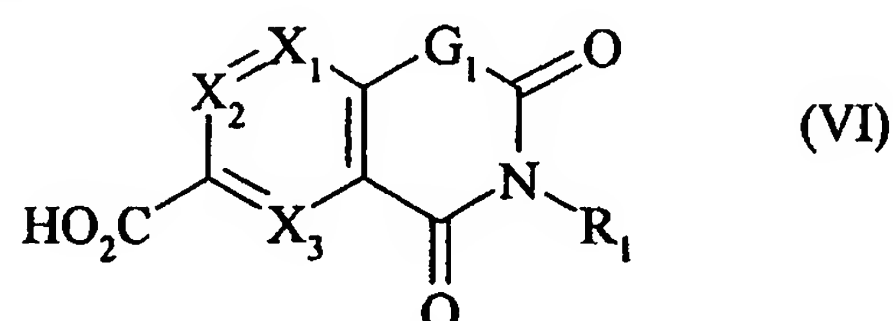
compound of formula (IV) in which the leaving group X is reacted with a cyanocuprate to yield the compound of formula (V) :

37



in which X_1 , X_2 , X_3 , G_1 , and R_1 are as defined hereinbefore,

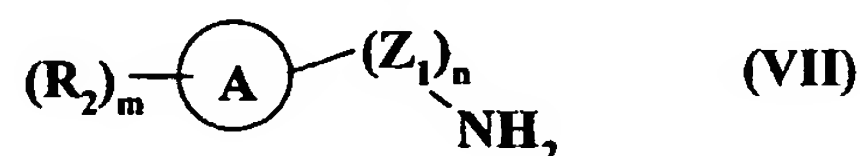
which compound of formula (V) is treated with an acid like sulfuric acid to yield the compound of formula (VI):



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in which X_1 , X_2 , X_3 , G_1 , and R_1 are as defined hereinbefore,

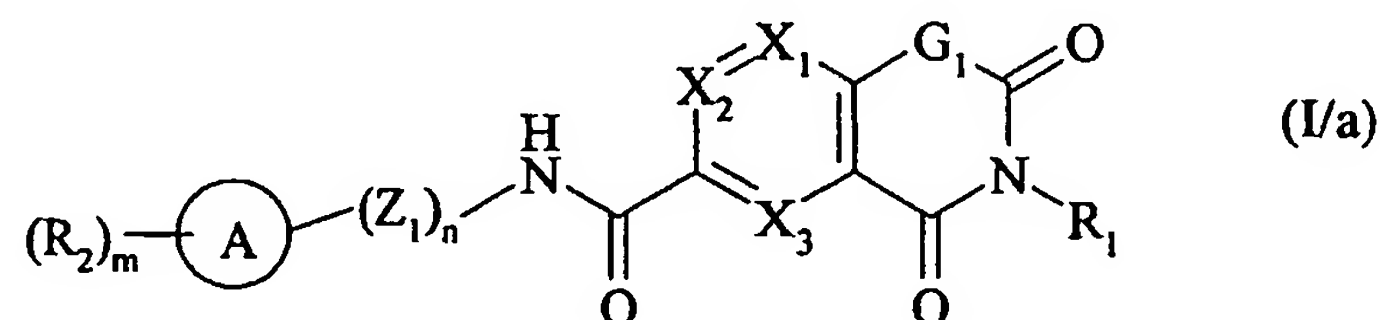
compound of formula (VI) which is treated with a compound of formula (VII):



in which Z_1 , R_2 , A , n and m have the same definitions as the compound of formula (I),

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by activating the acid function with an activator, in the presence of diisopropylethylamine and a solvent, to yield the compound of formula (I/a) which is a particular case of the compounds of formula (I):



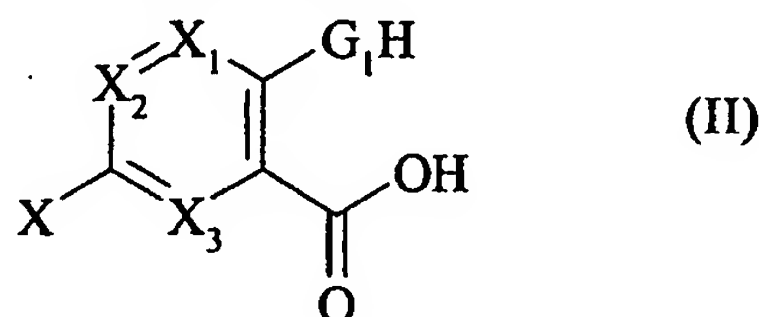
in which X_1 , X_2 , X_3 , G_1 , Z_1 , R_1 , R_2 , A , n and m are as defined hereinbefore,

5

compounds of formula (I/a) constitute some compounds of the invention, which are purified, where appropriate, according to a conventional purification technique, which are separated, where appropriate, into their different isomers according to a conventional

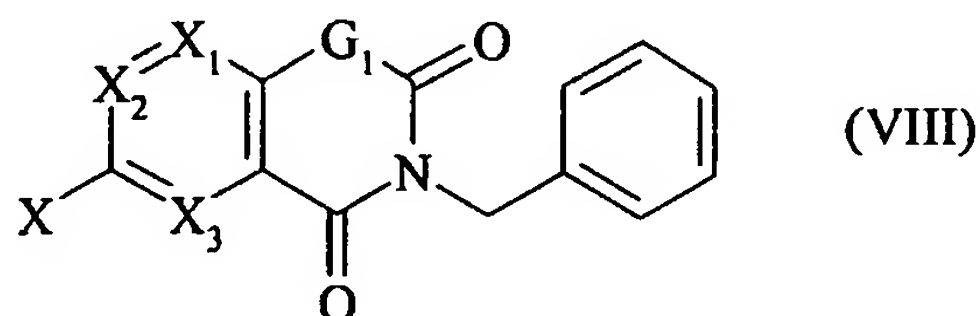
separation technique, and which are converted, where appropriate, into addition salts thereof with a pharmaceutically-acceptable acid or base, or into N-oxide thereof.

17- A process for the preparation of compounds according to claim 1 in which uses as starting material a compound of formula (II):



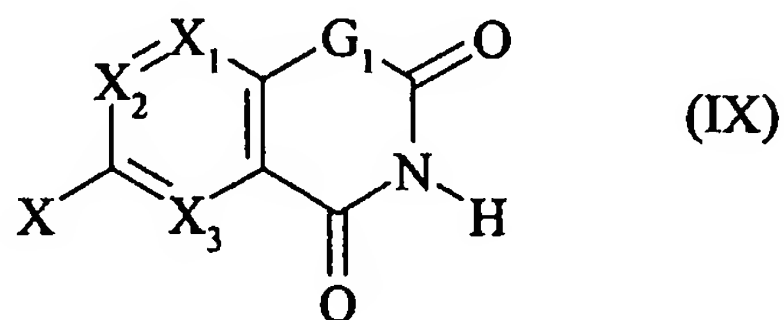
in which X_1 , X_2 , X_3 , and G_1 have the same definitions as the compound of formula (I), and X represents a leaving group selected from halogen, triflate, mesylate, tosylate and SO_2 alkyl,

compound of formula (II) which is treated in basic medium with a benzylisocyanate to yield the compound of formula (VIII) :



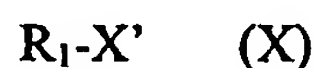
in which X_1 , X_2 , X_3 , G_1 , and X are as defined hereinbefore,

compound of formula (VIII) which is treated with $AlCl_3$ in an apolar solvent to yield the compound of formula (IX) :



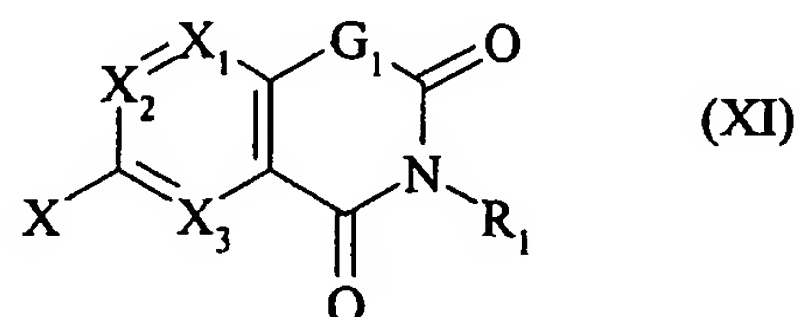
in which X_1 , X_2 , X_3 , G_1 , and X are as defined hereinbefore,

which compound of formula (IX) is treated in the presence of an inorganic base with a compound of formula (X):



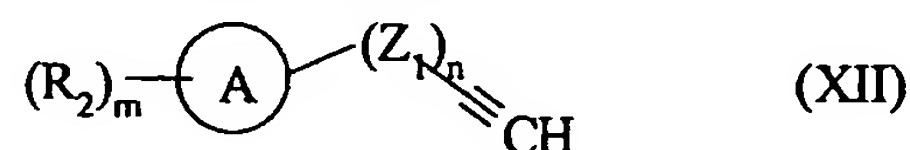
in which R_1 is as defined in the compound of formula (I) and X' represents a leaving group like halogen atom, mesylate, tosylate or triflate group,

to yield a compound of formula (XI) :



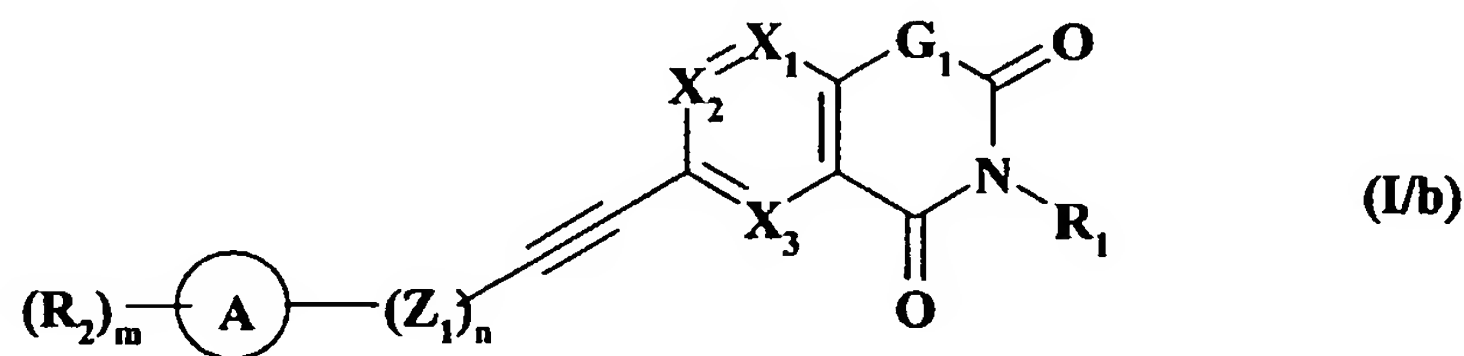
5 in which X_1 , X_2 , X_3 , G_1 , X and R_1 are as defined hereinbefore,

compound of formula (XI) which is condensed, in the presence of dichlorobis(triphenylphosphine)palladium, copper iodide and *N,N'*-diisopropylethylamine in dimethylformamide, on a compound of formula (XII) :



0 in which Z_1 , R_2 , A , n and m have the same definitions as the compound of formula (I),

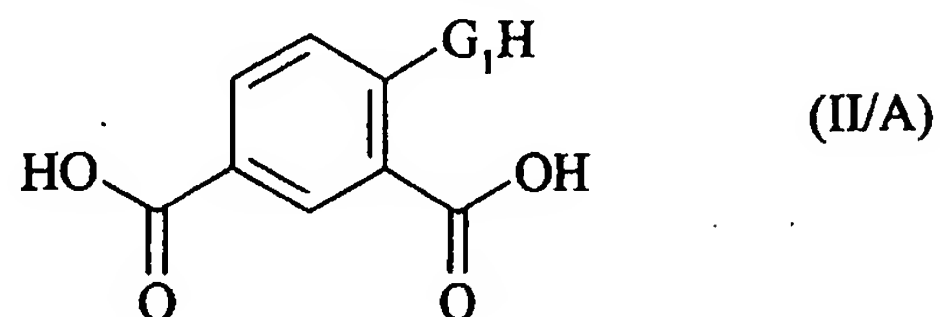
to yield the compound of formula (I/b), which is a particular case of the compound of formula (I):



in which X_1 , X_2 , X_3 , G_1 , Z_1 , R_1 , R_2 , A , n and m are as defined hereinbefore,

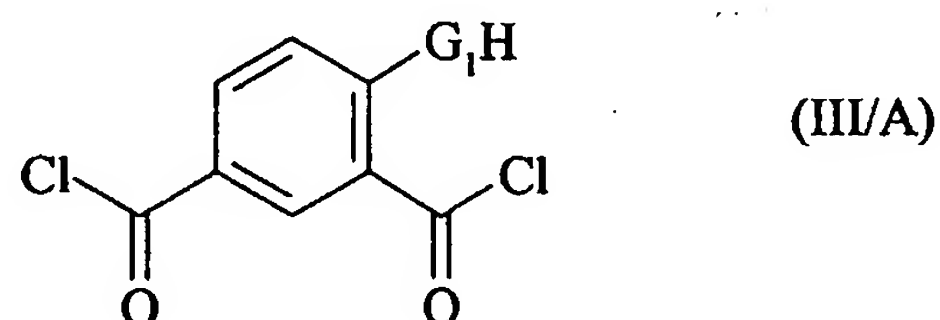
5 compounds of formula (I/b) constitute some compounds of the invention, which are purified, where appropriate, according to a conventional purification technique, which are separated, where appropriate, into their different isomers according to a conventional separation technique, and which are converted, where appropriate, into addition salts thereof with a pharmaceutically-acceptable acid or base, or into N-oxide thereof.

18 - A process for the preparation of compounds according to claim 1 in which uses as starting material a compound of formula (II/A):



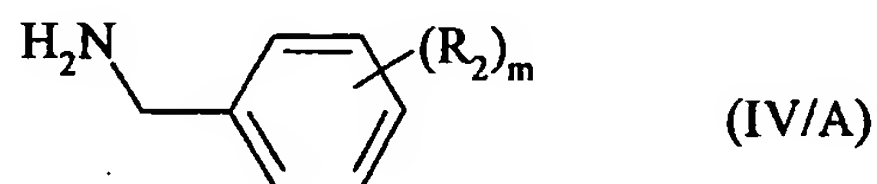
in which G_1 has the same definitions as the compound of formula (I),

5 compound of formula (II/A) which is treated with SOCl_2 to yield the compound of formula (III/A) :



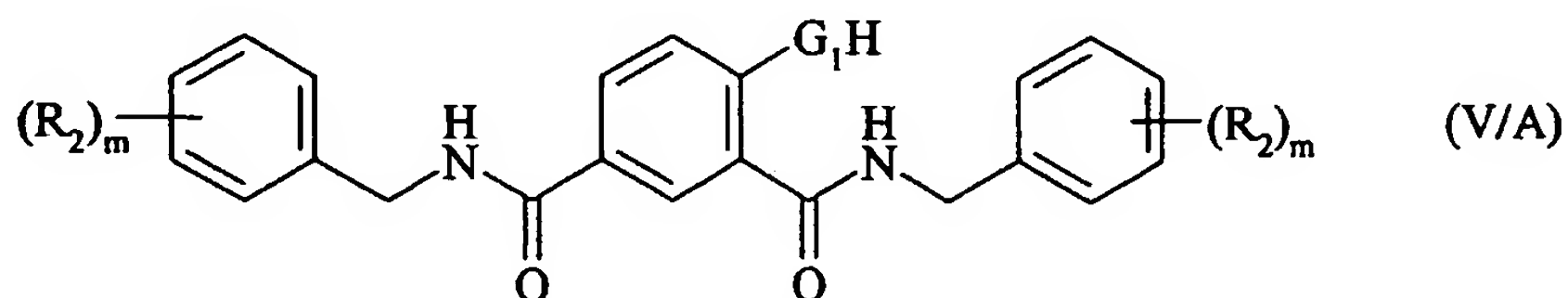
in which G_1 is as defined hereinbefore,

compound of formula (III/A) reacting with a benzylamine derivative of formula (IV/A):



in which R_2 and m are as defined in the compound of formula (I),

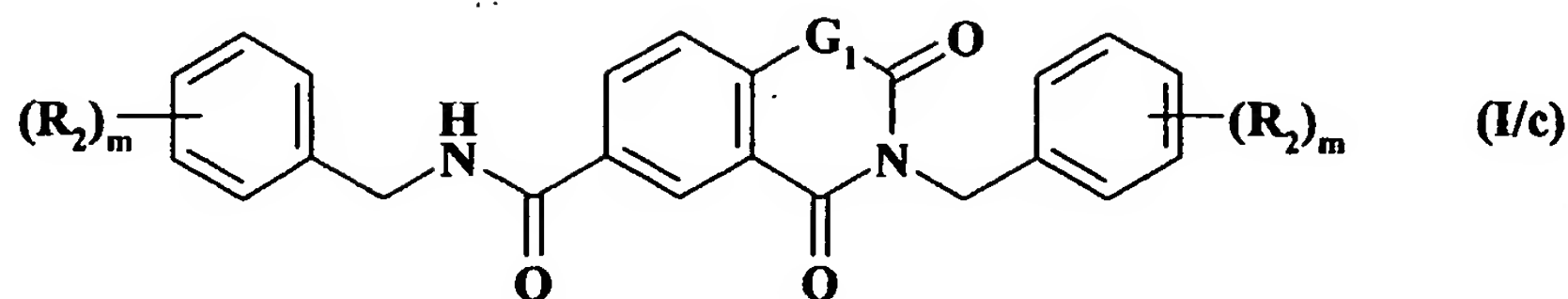
to yield the compound of formula (V/A):



in which G_1 , m and R_2 are as defined hereinbefore,

5 compound of formula (V/A) reacting with a chloroformate compound, to yield the compound of formula (I/c) which is a particular case of the compounds of formula (I):

41



in which G_1 , R_2 and m have the same definitions as the compound of formula (I), compounds of formula (I/c) constitute some compounds of the invention, which are purified, where appropriate, according to a conventional purification technique, which are separated, where appropriate, into their different isomers according to a conventional separation technique, and which are converted, where appropriate, into addition salts thereof with a pharmaceutically-acceptable acid or base, or into N-oxide thereof.

19- A method for treating a living body afflicted with a disease where the inhibition of type -13 matrix metalloprotease is involved, comprising the step of administering to the living body an amount of a compound of claim 1 which is effective for alleviation of said conditions.

20- A method for treating a living body afflicted with a disease selected from arthritis, rheumatoid arthritis, osteoarthritis, osteoporosis, periodontal diseases, inflammatory bowel disease, psoriasis, multiple sclerosis, cardiac insufficiency, atherosclerosis, asthma, chronic obstructive pulmonary disease, age-related macular degeneration, and cancers, comprising the step of administering to the living body an amount of a compound of claim 1 which is effective for alleviation of said conditions.

21- A pharmaceutical composition comprising as active ingredient an effective amount of a compound as claimed in claim 1, alone or in combination with one or more pharmaceutically-acceptable excipients or carriers.

22- A pharmaceutical composition useful in the method of Claim 19 comprising as active ingredient an effective amount of a compound as claimed in claim 1, together with one or more pharmaceutically-acceptable excipients or carriers.

- 23- A pharmaceutical composition useful in the method of Claim 19 comprising as active ingredient an effective amount of a compound as claimed in claim 2, together with one or more pharmaceutically-acceptable excipients or carriers.
- 24- A pharmaceutical composition useful in the method of Claim 19 comprising as active
5 ingredient an effective amount of a compound as claimed in claim 4, together with one or more pharmaceutically-acceptable excipients or carriers.
- 25- Use of a compound according to Claim 1, for the preparation of a medicinal product intended for treating a disease involving therapy by inhibition of type-13 matrix metalloproteases.
- 0 26- Use according to Claim 25, characterized in that the disease is arthritis, rheumatoid arthritis, osteoarthritis, osteoporosis, periodontal diseases, inflammatory bowel disease, psoriasis, multiple sclerosis, cardiac insufficiency, atherosclerosis, asthma, chronic obstructive pulmonary disease, age-related macular degeneration, and cancers.
- 27- Use according to Claim 26, characterized in that the disease is arthritis.
- 5 28- Use according to Claim 26, characterized in that the disease is osteoarthritis.
- 29- Use according to Claim 26, characterized in that the disease is rheumatoid arthritis.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 03/06601

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K31/536 A61K31/5415 A61P19/02 C07D279/08 C07D265/26

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 4 140 532 A (SATO HIDEO ET AL) 20 February 1979 (1979-02-20) General formula (I)	1,9-11
A	CHOLLET ET AL.: "Solid-phase synthesis of alpha-substituted 3-bisarylthio N-hydroxy propionamides as specific MMP inhibitors" BIOORGANIC AND MEDICINAL CHEMISTRY, vol. 10, no. 3, 2002, pages 531-544, XP002224266 Example 2-14	1-27
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☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *Z* document member of the same patent family

Date of the actual completion of the international search

8 October 2003

Date of mailing of the international search report

24/10/2003

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Johnson, C

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 03/06601

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>MONTANA J ET AL: "THE DESIGN OF SELECTIVE NON-SUBSTRATE-BASED MATRIX METALLOPROTEINASE INHIBITORS" CURRENT OPINION IN DRUG DISCOVERY AND DEVELOPMENT, CURRENT DRUGS, LONDON, GB, vol. 3, 2000, pages 353-361, XP000984034 ISSN: 1367-6733 the whole document</p>	1-27

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 03/06601

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 19,20 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this International application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

Information on patent family members

PCT/EP 03/06601

Form PCT/ISA/210 (patent family annex) (July 1992)